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- (74) Agents: SWISS, Gerald, F. et al.; Burns, Doane, Swecker & Mathis, L.L.P., P.O. Box 1404, Alexandria, VA 22313-1404 (US).
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- (71) Applicant (*for all designated States except US*): ADVANCED MEDICINE, INC. [US/US]; 901 Gateway Boulevard, South San Francisco, CA 94080 (US).
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- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): THOMAS, G., Roger [US/US]; 812 Park Avenue, Burlingame, CA 94010 (US). JENKINS, Thomas, E. [US/US]; 190 Canada Vista Drive, La Honda, CA 94131 (US). GRIFFIN, John, H. [US/US]; 56 Walnut Avenue, Atherton, CA 94027 (US).
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(54) Title: MULTIBINDING AGENTS THAT MODULATE NMDA RECEPTORS

(57) Abstract: Disclosed are novel multi-binding compounds (agents) which bind to NMDA receptors. The compounds of this invention comprise a plurality of ligands each of which can bind to such receptors, thereby modulating the biological processes and/or functions thereof. Each of the ligands is covalently attached to a linker or linkers which may be the same or different to provide for the multibinding compound. The linker is selected such that the multibinding compound so constructed demonstrates increased modulation of the biological processes mediated by the NMDA receptor.

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## MULTIBINDING AGENTS THAT MODULATE NMDA RECEPTORS

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### CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of United States Provisional Serial Number 60/088,466, filed June 8, 1998, and United States Provisional Serial  
10 Number 60/092,938, filed July 15, 1998.

### BACKGROUND OF THE INVENTION

#### Field of the Invention

This invention relates to novel therapeutic agents which bind to mammalian receptors and modulate their activity. More particularly, the invention relates to  
15 novel therapeutic agents that bind to and modulate the *in vivo* activity of the NMDA receptor in mammals by acting as multi-binding compounds. The therapeutic agents or multi-binding compounds described herein comprise at least two ligands connected by a linker or linkers, wherein said ligands in their monovalent state bind to and/or are capable of modulating the activity of the  
20 NMDA receptor. The linking moiety is chosen such that the multi-binding compounds so constructed demonstrate increased biological activity as compared to the same number of individual units of the ligand or ligands. The invention also relates to methods of using such compounds, to methods of preparing such compounds and to pharmaceutical compositions containing them.

25 These multi-binding compounds are particularly useful in treating mammalian conditions that are mediated by the NMDA receptors targeted by the ligands, such as pain sensation, Alzheimer's, cognitive disorder, dementia, schizophrenia, ocular disease, AIDS-related complex, peripheral neuropathy, CV



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ischemia, infarction, stroke, motor neuron disease, epilepsy, seizure, convulsions, neurodegenerative disease, micturation disorders, migraine, Parkinson's disease, psychosis, Huntingdon's chorea and cardiac failure. Accordingly, this invention also relates to pharmaceutical compositions comprising a pharmaceutically acceptable excipient and an effective amount of a multi-binding compound of this invention.

Publications cited herein are incorporated by reference in their entirety to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference in its entirety.

#### 10 State of the Art

A receptor is a biological structure with one or more binding domains that reversibly complexes with one or more ligands, where that complexation has biological consequences.

Receptors can exist entirely outside the cell (extracellular receptors), within the cell membrane (but presenting sections of the receptor to the extracellular milieu and cytosol), or entirely within the cell (intracellular receptors). They may also function independently of a cell (e.g., clot formation). Receptors within the cell membrane allow a cell to communicate with the space outside of its boundaries (i.e., signaling) as well as to function in the transport of molecules and ions into and out of the cell.

A ligand is a binding partner for a specific receptor or family of receptors. A ligand may be the endogenous ligand for the receptor or alternatively may be a synthetic ligand for the receptor such as a drug, a drug candidate or a pharmacological tool.

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The ligands that bind to cellular receptors may be specifically classified as follows:

1. Full agonists - ligands that when bound trigger the maximum activity seen by natural ligands;
- 5        2. Partial agonists- ligands that when bound trigger sub-maximal activity;
3. Antagonist- ligands that when bound inhibit or prevent the activity arising from a natural ligand binding to the receptor. Antagonists may be of the surmountable class (results in the parallel displacement of the dose-response curve of the agonist to the right in a dose dependent fashion without reducing the
- 10       maximal response for the agonist) or insurmountable class (results in depression of the maximal response for a given agonist with or without the parallel shift);
4. Inverse antagonist-ligands that when bound decrease the basal activity of the unbound receptor (if any).

There are four fundamental measurable properties that pertain to the

15       interaction of a ligand with its receptor:

- 1) the affinity of the ligand for the receptor, which relates to the energetics of the binding;
- 2) the efficacy of the ligand for the receptor, which relates to the functional downstream activity of the ligand;
- 20       3) the kinetics of the ligand for the receptor, which defines the onset of action and the duration of action; and
- 4) the desensitization of the receptor for the ligand.

With regard to the ligand, it is the combination of these properties that provides the foundation for defining the nature of the functional response. Thus,

25       an activating ligand (or agonist) has affinity for the receptor and downstream efficacy. In contrast, an inhibiting ligand (antagonist) has affinity for the receptor but no efficacy.

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Selectivity defines the ratios of affinities or the ratios of efficacies of a given ligand compared across two receptors. It is the selectivity of a specific drug that provides the required biological profile.

- 5      Current drugs (ligands) targeting NMDA receptors have clinical shortcomings identified by one or more of low efficacy, low affinity, poor safety profile, lack of selectivity or overselectivity for the intended receptor, and suboptimal duration of action and onset of action. Accordingly, it would be beneficial to develop ligands that have improved affinity, efficacy, selectivity, onset of action and duration of action.

10      Affinity of ligand for target receptor

An increase in ligand affinity to the target receptor may contribute to reducing the dose of ligand required to induce the desired therapeutic effect. A reduction in ligand affinity will remove activity and may contribute to the selectivity profile for a ligand.

15      Efficacy of ligand at a target receptor (functional effect)

- An increased ligand efficacy at a target receptor can lead to a reduction in the dose required to mediate the desired therapeutic effect. For example, this increase in efficacy may arise from an improved positive functional response of the ligand or a change from a partial to full agonist profile. Reduced efficacy of a full  
20      agonist to a partial agonist or antagonist may provide clinical benefit by modulating the biological response.

Selectivity of ligand compared across receptor subtypes

- An increase in the selectivity of the ligand across receptor subtypes requires that the affinity or efficacy of the ligand at other receptors is reduced  
25      relative to the desired receptor.

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Onset of Action

More rapid onset of action of the ligand to effect a biological response is often preferred.

Duration of Action

5 An increased duration of action of the ligand to effect a biological response may be preferred. For example  $\beta_2$  adrenergic agonists such as albuterol have a relatively short duration of action of approximately 3-4 hours and an increase in duration of action would simplify the dosing regimen required to administer this drug (ligand).

10 NMDA Receptor

The NMDA receptor belongs to the family of ligand-gated ion channels, as described by Kemp et al., in Drugs Pharm. Sci. (1998) Vol. 89 (Receptor based Drug Design) pp. 297-321. The NMDA receptor is a ligand-gated ion channel controlled by the binding of glutamate and glycine, wherein glutamate functions as a neurotransmitter and glycine functions as a modulator, with negative allosteric interaction between glutamate and glycine binding sites. L-Glutamate is a major excitatory transmitter of the mammalian central nervous system. The NMDA receptor is also activated by the binding of N-methyl-D-aspartate, and controls the transport of calcium and sodium. It is located primarily in the brain and spinal cord.

20 The NMDA receptor comprises a family of heteromers, each of which contain 5 subunits comprising an NMDAR1 subunit and four NR2 subunits which may be any of NR2<sub>A</sub>, NR2<sub>B</sub>, NR2<sub>C</sub> or NR2<sub>D</sub>. This combinatorial composition allows for subtype-specific compounds to be developed, which may affect one

25 NMDAR1/(NR2<sub>x</sub>)<sub>4</sub> combination and not another.

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The NMDA receptor plays a key role in neurotransmission, affecting physiological functions, and neuropathological states or conditions, such as epilepsy and acute neurodegeneration. It is known that the NMDA receptor may affect many different physiological and neuropathological functions associated with various conditions, including pain sensation, Alzheimer's, cognitive disorder, dementia, schizophrenia, ocular disease, AIDS-related complex, peripheral neuropathy, CV ischemia, infarction, stroke, motor neuron disease, epilepsy, seizure, convulsions, neurodegenerative disease, micturition disorders, migraine, Parkinson's disease, psychosis, Huntingdon's chorea and cardiac failure. Other conditions may also be associated with modulation of the NMDA receptor. Thus, modulation of the NMDA receptor to achieve desired effects in each of the above conditions is desirable.

It has been found that modulation of the NMDA receptor can lead to neurotoxic and other highly undesirable side effects. For example, neurotoxic effects caused by NMDA receptor agonists appear to be associated with the high permeability to calcium, high affinity for glutamate and lack of desensitization over prolonged activation of the NMDA receptor. On the other hand, total blockade of the NMDA receptor with noncompetitive antagonists is known to cause such profound central nervous systems effects as light headedness, dizziness, paresthesia, agitation, nystagmus, hallucinations, somnolence, increase in blood pressure, catatonia and dissociative anaesthesia.

The NMDA receptor is susceptible to activity by many different potential agonists, partial agonists and antagonists due to a multiplicity of binding sites. The NMDA receptor is activated by the combined binding of both a glutamate and glycine ligand. The activation of the receptor opens the cation channel, creating a potential binding site for an ion channel blocker. Further, it has been shown that The NMDA receptor can receive polyamine ligands, has a zinc binding site and a

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magnesium binding site, is subject to phosphorylation and has a redox site. Activation or modulation of any of the sites affects various changes in the activity of the NMDA receptor.

Accordingly, novel ligands having desired potency for and therapeutic effects at the NMDA receptor would be particularly desirable in order to modulate the cation transport activity of the NMDA receptor, especially in the case of pain in mammalian patients. Such novel ligands would preferably achieve the desired potency and therapeutic effect by modulating one or more of the ligand's properties as to efficacy, affinity, safety profile, selectivity, duration of action and/or onset of action. This may have advantages in the effects on other disease states as well, such as Alzheimer's, cognitive disorder, dementia, schizophrenia, ocular disease, AIDS-related complex, peripheral neuropathy, CV ischemia, infarction, stroke, motor neuron disease, epilepsy, seizure, convulsions, neurodegenerative disease, micturition disorders, migraine, Parkinson's disease, psychosis, Huntingdon's chorea and cardiac failure.

### SUMMARY OF THE INVENTION

This invention is directed to general synthetic methods for generating large libraries of diverse multimeric compounds which multimeric compounds are candidates for possessing multibinding properties. The diverse multimeric compound libraries provided by this invention are synthesized by combining a linker or linkers with a ligand or ligands to provide for a library of multimeric compounds wherein the linker and ligand each have complementary functional groups permitting covalent linkage. The library of linkers is preferably selected to have diverse properties such as valency, linker length, linker geometry and rigidity, hydrophilicity or hydrophobicity, amphiphilicity, acidity, basicity and polarization. The library of ligands is preferably selected to have diverse

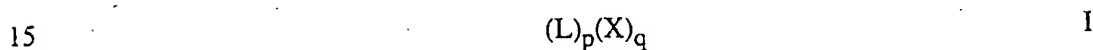
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attachment points on the same ligand, different functional groups at the same site of otherwise the same ligand, and the like.

This invention is also directed to libraries of diverse multimeric compounds which multimeric compounds are candidates for possessing multibinding properties. These libraries are prepared via the methods described above and permit the rapid and efficient evaluation of what molecular constraints impart multibinding properties to a ligand or a class of ligands targeting a receptor.

Accordingly, in one of its compositional aspects, this invention is directed to multi-binding compounds and salts thereof comprising 2 to 10 ligands, which may be the same or different and which are covalently attached to a linker or linkers which may be the same or different, at least one of said ligands comprising a ligand domain capable of binding to a NMDA receptor.

The multi-binding compounds of this invention are preferably represented by formula I:



wherein each L is independently selected from ligands comprising a ligand domain capable of binding to a NMDA receptor; X is independently a linker;  $p$  is an integer of from 2 to 10;  $q$  is an integer of from 1 to 20; and pharmaceutically acceptable salts thereof. Preferably,  $q$  is less than  $p$ .

20 In another of its composition aspects, this invention is directed to a pharmaceutical composition comprising a pharmaceutically acceptable excipient and an effective amount of a multi-binding compound, or a pharmaceutically acceptable salt thereof, comprising 2 to 10 ligands which may be the same or different and which are covalently attached to a linker or linkers which may be the

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same or different, at least one of said ligands comprising a ligand domain capable of binding to a NMDA receptor.

Preferably, said ligands comprising a ligand domain capable of binding to a NMDA receptor modulate cation transport, particularly calcium and sodium transport, in mammals. More preferably, said ligands are selected from the group consisting of L-689560, felbamate, L-701324, HA 966, L-687414, ifenprodil, eliprodil, RO-25-6981, nylidrin, SYM 2030, cycloserine, CGP-37489, CP-101606, arcaine, memantidine, dextrorphan, detromethorphan, remacemide, ketamine, ARL 15896AR, aptiganel, MK801, CNS-5161, selfotel, flupertine, SDZ EAA 494, ketobemidone, MDL 10043, CGP-40116, NPC 12626, FR 115427, MDL 27266, licostinel, L-705022, and BIII 227Cl, and derivatives thereof. In all embodiments, at least one ligand has a ligand binding domain capable of binding to a NMDA receptor.

In still another of its composition aspects, this invention is directed to a pharmaceutical composition comprising a pharmaceutically acceptable excipient and an effective amount of a multi-binding compound represented by formula I:



wherein each L is independently selected from ligands comprising a ligand domain capable of binding to a NMDA receptor; X is a linker;  $p$  is an integer of from 2 to 10;  $q$  is an integer of from 1 to 20; and pharmaceutically acceptable salts thereof. Preferably,  $q$  is less than  $p$ , and more preferably the ligand is selected from the group consisting of L-689560, felbamate, L-701324, HA 966, L-687414, ifenprodil, eliprodil, RO-25-6981, nylidrin, SYM 2030, cycloserine, CGP-37489, CP-101606, arcaine, memantidine, dextrorphan, detromethorphan, remacemide, ketamine, ARL 15896AR, aptiganel, MK801, CNS-5161, selfotel, flupertine, SDZ



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EAA 494, ketobemidone, MDL 10043, CGP-40116, NPC 12626, FR 115427, MDL 27266, licostinel, L-705022, and BIII 227Cl, and derivatives thereof.

In one of its method aspects, this invention is directed to a method for modulating cation transport by a NMDA receptor in a mammal, which method comprises administering to said mammal an effective amount of a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a multi-binding compound, or a pharmaceutically acceptable salt thereof, comprising 2 to 10 ligands which may be the same or different and which are covalently attached to a linker or linkers which may be the same or different, at least two of said ligands comprising a ligand domain capable of binding to a NMDA receptor.

In another of its method aspects, this invention is directed to a method for treating diseases or conditions including pain sensation, Alzheimer's, cognitive disorder, dementia, schizophrenia, ocular disease, AIDS-related complex, peripheral neuropathy, CV ischemia, infarction, stroke, motor neuron disease, epilepsy, seizure, convulsions, neurodegenerative disease, micturition disorders, migraine, Parkinson's disease, psychosis, Huntingdon's chorea and cardiac failure, particularly pain sensation, in a mammal mediated by NMDA receptors which method comprises administering to said mammal an effective amount of a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a multi-binding compound represented by formula I:



wherein each L is independently selected from ligands comprising a ligand domain capable of binding to a NMDA receptor mediating cation transport; X is a linker;  $p$  is an integer of from 2 to 10;  $q$  is an integer of from 1 to 20 and pharmaceutically acceptable salts thereof.

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Preferably,  $q$  is less than  $p$ , and more preferably, the ligand is selected from the group consisting of ligands having a ligand binding domain capable of binding to a NMDA receptor as set forth in detail herein.

- Accordingly, in one of its method aspects, this invention is directed to a
- 5 method for identifying multimeric ligand compounds possessing multibinding properties which method comprises:
- (a) identifying a ligand or a mixture of ligands wherein each ligand contains at least one reactive functionality;
  - (b) identifying a library of linkers wherein each linker in said library
  - 10 comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand;
  - (c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the ligand or mixture of ligands identified in (a) with the library of linkers identified in (b) under conditions wherein the
  - 15 complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands; and
  - (d) assaying the multimeric ligand compounds produced in (c) above to identify multimeric ligand compounds possessing multibinding properties.

- In another of its method aspects, this invention is directed to a method
- 20 for identifying multimeric ligand compounds possessing multibinding properties which method comprises:
- (a) identifying a library of ligands wherein each ligand contains at least one reactive functionality;
  - (b) identifying a linker or mixture of linkers wherein each linker
  - 25 comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand;

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(c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the library of ligands identified in (a) with the linker or mixture of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands; and

(d) assaying the multimeric ligand compounds produced in (c) above to identify multimeric ligand compounds possessing multibinding properties.

The preparation of the multimeric ligand compound library is achieved by either the sequential or concurrent combination of the two or more stoichiometric equivalents of the ligands identified in (a) with the linkers identified in (b). Sequential addition is preferred when a mixture of different ligands is employed to ensure heterodimeric or multimeric compounds are prepared. Concurrent addition of the ligands is preferred when at least a portion of the multimeric compounds prepared are homomultimeric compounds.

The assay protocols recited in (d) can be conducted on the multimeric ligand compound library produced in (c) above, or preferably, each member of the library is isolated by preparative liquid chromatography mass spectrometry (LCMS).

In one of its composition aspects, this invention is directed to a library of multimeric ligand compounds which may possess multivalent properties which library is prepared by the method comprising:

(a) identifying a ligand or a mixture of ligands wherein each ligand contains at least one reactive functionality;

(b) identifying a library of linkers wherein each linker in said library comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand; and

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- (c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the ligand or mixture of ligands identified in (a) with the library of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands.

In another of its composition aspects, this invention is directed to a library of multimeric ligand compounds which may possess multivalent properties which library is prepared by the method comprising:

- (a) identifying a library of ligands wherein each ligand contains at least one reactive functionality;
- (b) identifying a linker or mixture of linkers wherein each linker comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand; and
- (c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the library of ligands identified in (a) with the linker or mixture of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands.

In a preferred embodiment, the library of linkers employed in either the methods or the library aspects of this invention is selected from the group comprising flexible linkers, rigid linkers, hydrophobic linkers, hydrophilic linkers, linkers of different geometry, acidic linkers, basic linkers, linkers of different polarization and/or polarizability and amphiphilic linkers. For example, in one embodiment, each of the linkers in the linker library may comprise linkers of different chain length and/or having different complementary reactive groups. Such linker lengths can preferably range from about 2 to 100Å.

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In another preferred embodiment, the ligand or mixture of ligands is selected to have reactive functionality at different sites on said ligands in order to provide for a range of orientations of said ligand on said multimeric ligand compounds. Such reactive functionality includes, by way of example, carboxylic acids, carboxylic acid halides, carboxyl esters, amines, halides, pseudohalides, isocyanates, vinyl unsaturation, ketones, aldehydes, thiols, alcohols, anhydrides, boronates and precursors thereof. It is understood, of course, that the reactive functionality on the ligand is selected to be complementary to at least one of the reactive groups on the linker so that a covalent linkage can be formed between the linker and the ligand.

In other embodiments, the multimeric ligand compound is homomeric (i.e., each of the ligands is the same ligand having a ligand binding domain capable of binding to a NMDA receptor, although it may be attached at different points) or heteromeric (i.e., at least one of the ligands is different from the other ligands).

In addition to the combinatorial methods described herein, this invention provides for an iterative process for rationally evaluating what molecular constraints impart multibinding properties to a class of multimeric compounds or ligands targeting a receptor. Specifically, this method aspect is directed to a method for identifying multimeric ligand compounds possessing multibinding properties which method comprises:

- (a) preparing a first collection or iteration of multimeric compounds which is prepared by contacting at least two stoichiometric equivalents of the ligand or mixture of ligands which target a receptor with a linker or mixture of linkers wherein said ligand or mixture of ligands comprises at least one reactive functionality and said linker or mixture of linkers comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand wherein said contacting is conducted under conditions

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wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands;

(b) assaying said first collection or iteration of multimeric compounds to assess which if any of said multimeric compounds possess multibinding properties;

(c) repeating the process of (a) and (b) above until at least one multimeric compound is found to possess multibinding properties;

(d) evaluating what molecular constraints imparted multibinding properties to the multimeric compound or compounds found in the first iteration recited in (a)- (c) above;

(e) creating a second collection or iteration of multimeric compounds which elaborates upon the particular molecular constraints imparting multibinding properties to the multimeric compound or compounds found in said first iteration;

(f) evaluating what molecular constraints imparted enhanced multibinding properties to the multimeric compound or compounds found in the second collection or iteration recited in (e) above;

(g) optionally repeating steps (e) and (f) to further elaborate upon said molecular constraints.

Preferably, steps (e) and (f) are repeated at least two times, more preferably at least from 2-50 times, even more preferably from at least 3 to 50 times, and still more preferably at least 5-50 times.

### DETAILED DESCRIPTION OF THE INVENTION

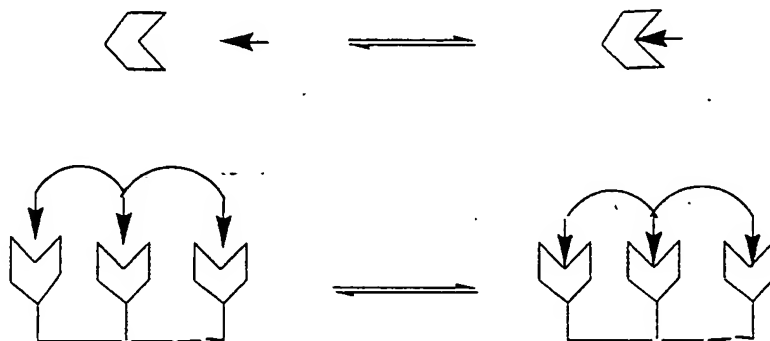
Ligand (drug) interactions with cellular receptors are controlled by molecular interaction/recognition between the ligand and the receptor. In turn, such interaction can result in modulation or disruption of the biological processes/functions of these receptors and, in some cases, leads to cell death. Accordingly, when cellular receptors mediate mammalian pathologic conditions,

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interactions of the ligand with the cellular receptor can be used to treat these conditions. Of particular interest are mammalian NMDA receptors which are known to affect cation transport, especially calcium and sodium transport, as well as other important functions. As noted above, this invention is directed, in part, to multi-binding compounds that bind NMDA receptors.

The "affinity" and "specificity" of the NMDA receptors and ligands thereto are dependent upon the complementarity of molecular binding surfaces and the energetic costs of complexation. "Affinity" is sometimes quantified by the equilibrium constant of complex formation. Specificity relates to the difference in affinity between the same ligand binding to different ligand binding sites on the cellular receptor.

The multi-binding compounds of this invention are capable of acting as multi-binding agents and the surprising activity of these compounds arises at least in part from their ability to bind in a multivalent manner with mammalian NMDA receptors. Multivalent binding interactions are characterized by the concurrent interaction of multiple ligands with multiple ligand binding sites on NMDA receptors. Multivalent interactions differ from collections of individual monovalent interactions by imparting enhanced biological and/or therapeutic effect. Examples of multivalent binding interaction (e.g., trivalent) relative to a monovalent binding interaction is shown below:



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Just as multivalent binding can amplify binding affinities, it can also amplify differences in binding affinities, resulting in enhanced binding specificity as well as affinity.

Definitions:

5 Prior to discussing this invention in further detail, the following terms will first be defined.

The term "alkyl" refers to a monoradical branched or unbranched saturated hydrocarbon chain preferably having from 1 to 40 carbon atoms, more preferably 1 to 10 carbon atoms, and even more preferably 1 to 6 carbon atoms. This term is exemplified by groups such as methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *n*-hexyl, *n*-decyl, tetradecyl, and the like.

The term "substituted alkyl" refers to an alkyl group as defined above, having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocycloxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocycloxy, hydroxy-amino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO<sub>2</sub>-alkyl, -SO<sub>2</sub>-substituted alkyl, -SO<sub>2</sub>-aryl and -SO<sub>2</sub>-heteroaryl.

The term "alkylene" refers to a diradical of a branched or unbranched saturated hydrocarbon chain, preferably having from 1 to 40 carbon atoms, more preferably 1 to 10 carbon atoms and even more preferably 1 to 6 carbon atoms. This term is exemplified by groups such as methylene (-CH<sub>2</sub>-), ethylene



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(-CH<sub>2</sub>CH<sub>2</sub>-), the propylene isomers (e.g., -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>- and -CH(CH<sub>3</sub>)CH<sub>2</sub>-) and the like.

The term "substituted alkylene" refers to an alkylene group, as defined above, having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocycloxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO<sub>2</sub>-alkyl, -SO<sub>2</sub>-substituted alkyl, -SO<sub>2</sub>-aryl and -SO<sub>2</sub>-heteroaryl. Additionally, such substituted alkylene groups include those where 2 substituents on the alkylene group are fused to form one or more cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heterocyclic or heteroaryl groups fused to the alkylene group. Preferably such fused groups contain from 1 to 3 fused ring structures.

The term "alkaryl" refers to the groups -alkylene-aryl and -substituted alkylene-aryl where alkylene, substituted alkylene and aryl are defined herein. Such alkaryl groups are exemplified by benzyl, phenethyl and the like.

The term "alkoxy" refers to the groups alkyl-O-, alkenyl-O-, cycloalkyl-O-, cycloalkenyl-O-, and alkynyl-O-, where alkyl, alkenyl, cycloalkyl, cycloalkenyl, and alkynyl are as defined herein. Preferred alkoxy groups are alkyl-O- and include, by way of example, methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *tert*-butoxy, *sec*-butoxy, *n*-pentoxy, *n*-hexoxy, 1,2-dimethylbutoxy, and the like.

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The term "substituted alkoxy" refers to the groups substituted alkyl-O-, substituted alkenyl-O-, substituted cycloalkyl-O-, substituted cycloalkenyl-O-, and substituted alkynyl-O- where substituted alkyl, substituted alkenyl, substituted cycloalkyl, substituted cycloalkenyl and substituted alkynyl are as defined herein.

5       The term "alkylalkoxy" refers to the groups -alkylene-O-alkyl, -alkylene-O-substituted alkyl, -substituted alkylene-O-alkyl and -substituted alkylene-O-substituted alkyl wherein alkyl, substituted alkyl, alkylene and substituted alkylene are as defined herein. Preferred alkylalkoxy groups are alkylene-O-alkyl and include, by way of example, methylenemethoxy  
10       (-CH<sub>2</sub>OCH<sub>3</sub>), ethylenemethoxy (-CH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>), *n*-propylene-*iso*-propoxy (-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>OCH(CH<sub>3</sub>)<sub>2</sub>), methylene-*t*-butoxy (-CH<sub>2</sub>-O-C(CH<sub>3</sub>)<sub>3</sub>) and the like.

The term "alkylthioalkoxy" refers to the group -alkylene-S-alkyl, alkylene-S-substituted alkyl, substituted alkylene-S-alkyl and substituted alkylene-S-substituted alkyl wherein alkyl, substituted alkyl, alkylene and substituted  
15       alkylene are as defined herein. Preferred alkylthioalkoxy groups are alkylene-S-alkyl and include, by way of example, methylenethiomethoxy (-CH<sub>2</sub>SCH<sub>3</sub>), ethylenethiomethoxy (-CH<sub>2</sub>CH<sub>2</sub>SCH<sub>3</sub>), *n*-propylene-*iso*-thiopropoxy (-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SCH(CH<sub>3</sub>)<sub>2</sub>), methylene-*t*-thiobutoxy (-CH<sub>2</sub>SC(CH<sub>3</sub>)<sub>3</sub>) and the like.

20       The term "alkenyl" refers to a monoradical of a branched or unbranched unsaturated hydrocarbon group preferably having from 2 to 40 carbon atoms, more preferably 2 to 10 carbon atoms and even more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-6 sites of vinyl unsaturation. Preferred alkenyl groups include ethenyl (-CH=CH<sub>2</sub>), *n*-propenyl (-CH<sub>2</sub>CH=CH<sub>2</sub>), *iso*-  
25       propenyl (-C(CH<sub>3</sub>)=CH<sub>2</sub>), and the like.

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The term "substituted alkenyl" refers to an alkenyl group as defined above having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocycloxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO<sub>2</sub>-alkyl, -SO<sub>2</sub>-substituted alkyl, -SO<sub>2</sub>-aryl and -SO<sub>2</sub>-heteroaryl.

The term "alkenylene" refers to a diradical of a branched or unbranched unsaturated hydrocarbon group preferably having from 2 to 40 carbon atoms, more preferably 2 to 10 carbon atoms and even more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-6 sites of vinyl unsaturation. This term is exemplified by groups such as ethenylene (-CH=CH-), the propenylene isomers (e.g., -CH<sub>2</sub>CH=CH- and -C(CH<sub>3</sub>)=CH-) and the like.

The term "substituted alkenylene" refers to an alkenylene group as defined above having from 1 to 5 substituents, and preferably from 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocycloxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO<sub>2</sub>-alkyl, -SO<sub>2</sub>-substituted alkyl, -SO<sub>2</sub>-aryl and -SO<sub>2</sub>-heteroaryl.

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Additionally, such substituted alkenylene groups include those where 2 substituents on the alkenylene group are fused to form one or more cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heterocyclic or heteroaryl groups fused to the alkenylene group.

5           The term "alkynyl" refers to a monoradical of an unsaturated hydrocarbon preferably having from 2 to 40 carbon atoms, more preferably 2 to 20 carbon atoms and even more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-6 sites of acetylene (triple bond) unsaturation. Preferred alkynyl groups include ethynyl ( $-C\equiv CH_2$ ), propargyl ( $-CH_2C\equiv CH$ ) and the like.

10           The term "substituted alkynyl" refers to an alkynyl group as defined above having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, 15 halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocycloxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocycloxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO<sub>2</sub>-alkyl, -SO<sub>2</sub>-substituted alkyl, -SO<sub>2</sub>-aryl and -SO<sub>2</sub>-heteroaryl.

20           The term "alkynylene" refers to a diradical of an unsaturated hydrocarbon preferably having from 2 to 40 carbon atoms, more preferably 2 to 10 carbon atoms and even more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-6 sites of acetylene (triple bond) unsaturation. Preferred alkynylene groups include ethynylene ( $-C\equiv C-$ ), propargylene ( $-CHC\equiv C-$ ) and the 25 like.

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The term "substituted alkynylene" refers to an alkynylene group as defined above having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocycloxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocycloxy, hydroxy-amino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO<sub>2</sub>-alkyl, -SO<sub>2</sub>-substituted alkyl, -SO<sub>2</sub>-aryl and -SO<sub>2</sub>-heteroaryl.

The term "acyl" refers to the groups HC(O)-, alkyl-C(O)-, substituted alkyl-C(O)-, cycloalkyl-C(O)-, substituted cycloalkyl-C(O)-, cycloalkenyl-C(O)-, substituted cycloalkenyl-C(O)-, aryl-C(O)-, heteroaryl-C(O)- and heterocyclic-C(O)- where alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic are as defined herein.

The term "acylamino" refers to the group -C(O)NRR where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, heterocyclic or where both R groups are joined to form a heterocyclic group (e.g., morpholino) wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

The term "aminoacyl" refers to the group -NRC(O)R where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

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The term "aminoacyloxy" refers to the group -NRC(O)OR where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

5       The term "acyloxy" refers to the groups alkyl-C(O)O-, substituted alkyl-C(O)O-, cycloalkyl-C(O)O-, substituted cycloalkyl-C(O)O-, aryl-C(O)O-, heteroaryl-C(O)O-, and heterocyclic-C(O)O- wherein alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl, and heterocyclic are as defined herein.

10       The term "aryl" refers to an unsaturated aromatic carbocyclic group of from 6 to 20 carbon atoms having a single ring (e.g., phenyl) or multiple condensed (fused) rings (e.g., naphthyl or anthryl). Preferred aryls include phenyl, naphthyl and the like.

15       Unless otherwise constrained by the definition for the aryl substituent, such aryl groups can optionally be substituted with from 1 to 5 substituents, preferably 1 to 3 substituents, selected from the group consisting of acyloxy, hydroxy, thiol, acyl, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkoxy, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted cycloalkenyl, amino, substituted amino, aminoacyl, acylamino, alkaryl,  
20       aryl, aryloxy, azido, carboxyl, carboxylalkyl, cyano, halo, nitro, heteroaryl, heteroaryloxy, heterocyclic, heterocycloxy, aminoacyloxy, oxyacylamino, thioalkoxy, substituted thioalkoxy, thioaryloxy, thioheteroaryloxy, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO<sub>2</sub>-alkyl, -SO<sub>2</sub>-substituted alkyl, -SO<sub>2</sub>-aryl, -SO<sub>2</sub>-heteroaryl and trihalomethyl. Preferred aryl substituents include  
25       alkyl, alkoxy, halo, cyano, nitro, trihalomethyl, and thioalkoxy.

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The term "aryloxy" refers to the group aryl-O- wherein the aryl group is as defined above including optionally substituted aryl groups as also defined above.

The term "arylene" refers to the diradical derived from aryl (including substituted aryl) as defined above and is exemplified by 1,2-phenylene, 1,3-phenylene, 1,4-phenylene, 1,2-naphthylene and the like.

The term "amino" refers to the group -NH<sub>2</sub>.

The term "substituted amino" refers to the group -NRR where each R is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl and heterocyclic provided that both R's are not hydrogen.

The term "carboxyalkyl" refers to the groups "-C(O)O-alkyl", "-C(O)O-substituted alkyl", "-C(O)O-cycloalkyl", "-C(O)O-substituted cycloalkyl", "-C(O)O-alkenyl", "-C(O)O-substituted alkenyl", "-C(O)O-alkynyl" and "-C(O)O-substituted alkynyl" where alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl and substituted alkynyl are as defined herein.

The term "cycloalkyl" refers to cyclic alkyl groups of from 3 to 20 carbon atoms having a single cyclic ring or multiple condensed rings. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclooctyl, and the like, or multiple ring structures such as adamantanyl, and the like.

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The term "substituted cycloalkyl" refers to cycloalkyl groups having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocycloxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO<sub>2</sub>-alkyl, -SO<sub>2</sub>-substituted alkyl, -SO<sub>2</sub>-aryl and -SO<sub>2</sub>-heteroaryl.

The term "cycloalkenyl" refers to cyclic alkenyl groups of from 4 to 20 carbon atoms having a single cyclic ring and at least one point of internal unsaturation. Examples of suitable cycloalkenyl groups include, for instance, cyclobut-2-enyl, cyclopent-3-enyl, cyclooct-3-enyl and the like.

The term "substituted cycloalkenyl" refers to cycloalkenyl groups having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocycloxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO<sub>2</sub>-alkyl, -SO<sub>2</sub>-substituted alkyl, -SO<sub>2</sub>-aryl and -SO<sub>2</sub>-heteroaryl.

The term "halo" or "halogen" refers to fluoro, chloro, bromo and iodo.



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The term "heteroaryl" refers to an aromatic group of from 1 to 15 carbon atoms and 1 to 4 heteroatoms selected from oxygen, nitrogen and sulfur within at least one ring (if there is more than one ring).

Unless otherwise constrained by the definition for the heteroaryl substituent, such heteroaryl groups can be optionally substituted with 1 to 5 substituents, preferably 1 to 3 substituents, selected from the group consisting of acyloxy, hydroxy, thiol, acyl, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkoxy, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted cycloalkenyl, amino, substituted amino, aminoacyl, acylamino, alkaryl, aryl, aryloxy, azido, carboxyl, carboxylalkyl, cyano, halo, nitro, heteroaryl, heteroaryloxy, heterocyclic, heterocycloxy, aminoacyloxy, oxyacylamino, thioalkoxy, substituted thioalkoxy, thioaryloxy, thioheteroaryloxy, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO<sub>2</sub>-alkyl, -SO<sub>2</sub>-substituted alkyl, -SO<sub>2</sub>-aryl, -SO<sub>2</sub>-heteroaryl and trihalomethyl.

Preferred aryl substituents include alkyl, alkoxy, halo, cyano, nitro, trihalomethyl, and thioalkoxy. Such heteroaryl groups can have a single ring (e.g., pyridyl or furyl) or multiple condensed rings (e.g., indolizinyll or benzothienyl). Preferred heteroaryls include pyridyl, pyrrolyl and furyl.

The term "heteroaryloxy" refers to the group heteroaryl-O-.

The term "heteroarylene" refers to the diradical group derived from heteroaryl (including substituted heteroaryl), as defined above, and is exemplified by the groups 2,6-pyridylene, 2,4-pyridylene, 1,2-quinolinyllene, 1,8-quinolinyllene, 1,4-benzofuranyllene, 2,5-pyridnyllene, 2,5-indolenyl and the like.

The term "heterocycle" or "heterocyclic" refers to a monoradical saturated unsaturated group having a single ring or multiple condensed rings, from 1 to 40

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carbon atoms and from 1 to 10 hetero atoms, preferably 1 to 4 heteroatoms, selected from nitrogen, sulfur, phosphorus, and/or oxygen within the ring.

Unless otherwise constrained by the definition for the heterocyclic substituent, such heterocyclic groups can be optionally substituted with 1 to 5, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocycloxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocycloxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO<sub>2</sub>-alkyl, -SO<sub>2</sub>-substituted alkyl, -SO<sub>2</sub>-aryl and -SO<sub>2</sub>-heteroaryl. Such heterocyclic groups can have a single ring or multiple condensed rings. Preferred heterocyclics include morpholino, piperidinyl, and the like.

Examples of nitrogen heterocycles and heteroaryls include, but are not limited to, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthylpyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole, phenoxazine, phenothiazine, imidazolidine, imidazoline, piperidine, piperazine, indoline, morpholino, piperidinyl, tetrahydrofuranyl, and the like as well as N-alkoxy-nitrogen containing heterocycles.

A preferred class of heterocyclics include "crown compounds" which refers to a specific class of heterocyclic compounds having one or more repeating

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units of the formula  $[-(\text{CH}_2)_m\text{Y}]$  where  $m$  is  $\geq 2$ , and Y at each separate occurrence can be O, N, S or P. Examples of crown compounds include, by way of example only,  $[-(\text{CH}_2)_3\text{-NH-}]_3$ ,  $[-((\text{CH}_2)_2\text{-O})_4-((\text{CH}_2)_2\text{-NH})_2]$  and the like. Typically such crown compounds can have from 4 to 10 heteroatoms and 8 to 40 carbon atoms.

The term "heterocyclooxy" refers to the group heterocyclic-O-.

The term "thioheterocyclooxy" refers to the group heterocyclic-S-.

The term "heterocyclene" refers to the diradical group formed from a heterocycle, as defined herein, and is exemplified by the groups 2,6-morpholino, 2,5-morpholino and the like.

The term "oxyacylamino" refers to the group  $-\text{OC}(\text{O})\text{NRR}$  where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

The term "pseudohalide" refers to functional groups which react in displacement reactions in a manner similar to a halogen. Such functional groups include, by way of example, mesyl, tosyl, azido and cyano groups.

The term "thiol" refers to the group -SH.

The term "thioalkoxy" refers to the group -S-alkyl.

The term "substituted thioalkoxy" refers to the group -S-substituted alkyl.

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The term "thioaryloxy" refers to the group aryl-S- wherein the aryl group is as defined above including optionally substituted aryl groups also defined above.

5 The term "thioheteroaryloxy" refers to the group heteroaryl-S- wherein the heteroaryl group is as defined above including optionally substituted aryl groups as also defined above.

As to any of the above groups which contain one or more substituents, it is understood, of course, that such groups do not contain any substitution or substitution patterns which are sterically impractical and/or synthetically non-feasible. In addition, the compounds of this invention include all stereochemical  
10 isomers arising from the substitution of these compounds.

The term "pharmaceutically acceptable salt" refers to salts which retain the biological effectiveness and properties of the multi-binding compounds of this invention and which are not biologically or otherwise undesirable. In many cases, the multi-binding compounds of this invention are capable of forming acid and/or  
15 base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto.

Pharmaceutically acceptable base addition salts can be prepared from inorganic and organic bases. Salts derived from inorganic bases, include by way of example only, sodium, potassium, lithium, ammonium, calcium and magnesium  
20 salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary and tertiary amines, such as alkyl amines, dialkyl amines, trialkyl amines, substituted alkyl amines, di(substituted alkyl) amines, tri(substituted alkyl) amines, alkenyl amines, dialkenyl amines, trialkenyl amines, substituted alkenyl amines, di(substituted alkenyl) amines, tri(substituted alkenyl)  
25 amines, cycloalkyl amines, di(cycloalkyl) amines, tri(cycloalkyl) amines.

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substituted cycloalkyl amines, disubstituted cycloalkyl amine, trisubstituted cycloalkyl amines, cycloalkenyl amines, di(cycloalkenyl) amines, tri(cycloalkenyl) amines, substituted cycloalkenyl amines, disubstituted cycloalkenyl amine, trisubstituted cycloalkenyl amines, aryl amines, diaryl amines, triaryl amines, 5 heteroaryl amines, diheteroaryl amines, triheteroaryl amines, heterocyclic amines, diheterocyclic amines, triheterocyclic amines, mixed di- and tri-amines where at least two of the substituents on the amine are different and are selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, 10 heteroaryl, heterocyclic, and the like. Also included are amines where the two or three substituents, together with the amino nitrogen, form a heterocyclic or heteroaryl group.

Examples of suitable amines include, by way of example only, isopropylamine, trimethyl amine, diethyl amine, tri(*iso*-propyl) amine, tri(*n*- 15 propyl) amine, ethanolamine, 2-dimethylaminoethanol, tromethamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, N-alkylglucamines, theobromine, purines, piperazine, piperidine, morpholine, N-ethylpiperidine, and the like. It should also be understood that other carboxylic acid derivatives would be useful in the practice 20 of this invention, for example, carboxylic acid amides, including carboxamides, lower alkyl carboxamides, dialkyl carboxamides, and the like.

Pharmaceutically acceptable acid addition salts may be prepared from inorganic and organic acids. Salts derived from inorganic acids include hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, 25 and the like. Salts derived from organic acids include acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid,

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mandelic acid, methanesulfonic acid, ethanesulfonic acid, *p*-toluene-sulfonic acid, salicylic acid, and the like.

The term "protecting group" or "blocking group" refers to any group which when bound to one or more hydroxyl, thiol, amino or carboxyl groups of the compounds (including intermediates thereof) prevents reactions from occurring at these groups and which protecting group can be removed by conventional chemical or enzymatic steps to reestablish the hydroxyl, thiol, amino or carboxyl group (Green, *Protective Groups in Organic Synthesis*, 2<sup>nd</sup> Ed., John Wiley & Sons, NY, NY (1991)). The particular removable blocking group employed is not critical and preferred removable hydroxyl blocking groups include conventional substituents such as allyl, benzyl, acetyl, chloroacetyl, thiobenzyl, benzylidene, phenacyl, *t*-butyl-diphenylsilyl and any other group that can be introduced chemically onto a hydroxyl functionality and later selectively removed either by chemical or enzymatic methods in mild conditions compatible with the nature of the product.

Preferred removable amino blocking groups include conventional substituents such as *t*-butoxycarbonyl (*t*-BOC), benzyloxycarbonyl (CBZ), and the like which can be removed by conventional conditions compatible with the nature of the product.

Preferred carboxyl protecting groups include esters such as methyl, ethyl, propyl, *t*-butyl etc. which can be removed by mild hydrolysis conditions compatible with the nature of the product.

The term "optional" or "optionally" means that the subsequently described event, circumstance or substituent may or may not occur, and that the description

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includes instances where said event or circumstance occurs and instances where it does not.

As used herein, the terms "inert organic solvent" or "inert solvent" mean a solvent inert under the conditions of the reaction being described in conjunction therewith [including, for example, benzene, toluene, acetonitrile, tetrahydrofuran ("THF"), dimethylformamide ("DMF"), chloroform ( $\text{CHCl}_3$ ), methylene chloride (or dichloromethane or " $\text{CH}_2\text{Cl}_2$ "), diethyl ether, ethyl acetate, acetone, methylethyl ketone, methanol, ethanol, propanol, isopropanol, tert-butanol, dioxane, pyridine, and the like]. Unless specified to the contrary, the solvents used in the reactions of the present invention are inert solvents.

The "NMDA receptor" is a receptor which plays a role in cation transport, specifically calcium and sodium transport related to neuronal activity. NMDA receptors are located primarily in the brain and spinal cord.

It should be recognized that the NMDA receptors that participate in biological multivalent binding interactions are constrained to varying degrees by their intra- and intermolecular associations (e.g. cellular receptors may be covalently joined in a single structure, noncovalently associated in a multimeric structure, embedded in a membrane or polymeric matrix and so on) and therefore have less translational and rotational freedom than if the same cellular receptors were present as monomers in solution.

The term "library" refers to at least 3, preferably from  $10^2$  to  $10^9$  and more preferably from  $10^2$  to  $10^4$  multimeric compounds. Preferably, these compounds are prepared as a multiplicity of compounds in a single solution or reaction mixture which permits facile synthesis thereof. In one embodiment, the library of multimeric compounds can be directly assayed for multibinding

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properties. In another embodiment, each member of the library of multimeric compounds is first isolated and, optionally, characterized. This member is then assayed for multibinding properties.

5 The term "collection" refers to a set of multimeric compounds which are prepared either sequentially or concurrently (e.g., combinatorially). The collection comprises at least 2 members; preferably from 2 to  $10^9$  members and still more preferably from 10 to  $10^4$  members.

10 The term "ligand binding site" as used herein denotes the site on the NMDA receptor that recognizes a ligand domain and provides a binding partner for that ligand. The ligand binding site may be defined by monomeric or multimeric structures. This interaction may be capable of producing a unique biological effect, for example agonism, antagonism, modulatory effect and the like or may maintain an ongoing biological event.

15 "Ligand" as used herein denotes a compound that is a binding partner for the NMDA receptor and is bound thereto by complementarity. The specific region or regions of the ligand that is (are) recognized by the NMDA receptor is designated as the "ligand binding domain". A ligand may be either capable of binding to a receptor by itself, or may require the presence of one or more non-ligand components for binding (e.g.,  $\text{Ca}^{+2}$ ,  $\text{Mg}^{+2}$  or a water molecule).

20 It is further understood that the term "ligand" is not intended to be limited to compounds known to be useful as NMDA receptor binding compounds (e.g., known drugs). It should also be understood that portions of the ligand structure that are not essential for specific molecular recognition and binding activity may be varied substantially, replaced with unrelated structures and, in some cases,  
25 omitted entirely without affecting the binding interaction. The primary



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requirement for the ligand is that it has a ligand domain as defined above. Those skilled in the art will understand that the term ligand can equally apply to a molecule that is not normally associated with NMDA cellular receptor binding properties. In addition, it should be noted that ligands that exhibit marginal activity or lack useful activity as monomers can be highly active as multivalent compounds because of the benefits conferred by multi-valency. The only requirement for a ligand is that it has a ligand binding domain as defined above.

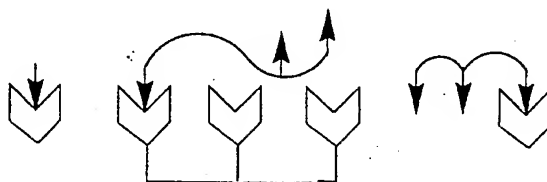
A "multimeric compound" refers to a compound that may be capable of multivalency as defined below, and which has 2 to 10 ligands covalently bound to one or more linkers which may be the same or different. The compound may or may not possess multibinding properties. At least one of the ligands comprises a ligand domain capable of binding to a NMDA receptor. The multi-binding compound provides a biological and/or therapeutic effect greater than the aggregate of unlinked ligands equivalent thereto which may be the same or different which unlinked ligands comprise a ligand domain capable of binding to NMDA receptors. That is to say that the biological and/or therapeutic effect of the ligands capable of binding to a NMDA receptor attached to the multi-binding compound is greater than that achieved by the same amount of unlinked ligands capable of binding to a NMDA receptor made available for binding to the ligand binding sites.

The phrase "increased biological or therapeutic effect" includes, for example increased affinity for a target, increased specificity for a target, increased selectivity for a target, increased potency, increased efficacy, decreased toxicity, improved duration of action, decreased side effects, increased therapeutic index, improved bioavailability, improved pharmacokinetics, improved activity spectrum, and the like. The multi-binding compounds of this invention will exhibit at least one and preferably more than one of the above mentioned effects.

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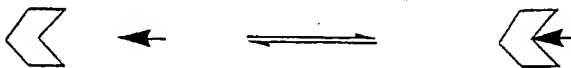
"Uni-valency" as used herein refers to a single binding interaction between one ligand as defined herein with one ligand binding site as defined herein. It should be noted that a molecule having multiple copies of a ligand (or ligands) exhibits uni-valency when only one ligand is interacting with a ligand binding site.

5 Examples of a univalent interaction are depicted below.



"Multi-valency" as used herein refers to the concurrent binding of from 2 to 10 linked ligands (which may be the same or different) and two or more corresponding ligand binding sites on the receptors which receptors may be the same or different.

10 For example, two ligands connected by a linker that bind concurrently to two ligand binding sites would be considered as bi-valency; three ligands thus connected would be an example of tri-valency. An example of tri-valency illustrating a multi-binding agent bearing three ligands versus a monovalent binding interaction is shown below:



15

univalent interaction

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trivalent interaction

It should be understood that all compounds that contain multiple copies of a ligand attached to a linker do not necessarily exhibit the phenomena of multivalency, i.e., that the biological and/or therapeutic effect of the multi-binding agent is greater than the sum of the aggregate of unlinked ligands made available to the ligand binding site. For multivalency to occur, the ligands that are connected by a linker have to be presented to their receptors by the linker in a specific manner in order to bring about the desired ligand-orienting result, and thus produce a multi-binding agent.

“Potency” as used herein refers to the minimum concentration at which a ligand is able to achieve a desirable biological or therapeutic effect. The potency of a ligand is typically proportional to its affinity for its ligand binding site. In some cases the potency may be non-linearly correlated with its affinity. In comparing the potency of two drugs, e.g., a multi-binding agent and the aggregate of its unlinked ligand, the dose-response curve of each is determined under identical test conditions (e.g. an *in vitro* or *in vivo* assay, in an appropriate animal model such as a human patient). The finding that the multi-binding agent produces an equivalent biological or therapeutic effect at a lower concentration than the aggregate unlinked ligand (e.g. on a per weight, per mole or per ligand basis) is indicative of enhanced potency.

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“Selectivity” or “specificity” is a measure of the binding preferences of a ligand for different ligand binding sites. The selectivity of a ligand with respect to its target ligand binding site relative to another ligand binding site is given by the ratio of the respective values of  $K_d$  (i.e., the dissociation constants for each ligand-receptor complex) or in cases where a biological effect is observed below the  $K_d$ , the ratio of the respective  $EC_{50}$ s (i.e., the concentrations that produce 50% of the maximum response for the ligand interacting with the two distinct ligand binding sites).

The terms “agonism” and “antagonism” are well known in the art. The term “modulatory effect” refers to the ability of the ligand to change the activity of an agonist or antagonist through binding to a ligand binding site.

The term “partial agonist” refers to a receptor agonist which cannot fully elicit a maximal response when it binds to the receptor, no matter how high the concentration of the partial agonist. A partial agonist is able to combine with the receptor, but the full effect of the binding is not elicited. This term is well known in the art and a discussion of it may be found in Textbook of Receptor Pharmacology, ch 1.4, J. Foreman and T. Johansen eds., CRC Press, 1996.

The term “treatment” refers to the treatment of pain in a mammal, particularly a human, and includes:

- (i) modulating the activity of the NMDA receptor;
- (ii) alleviating pain or lessening pain; and
- (iii) inhibiting pain.

The term “therapeutically effective amount” refers to that amount of multi-binding compound which is sufficient to effect treatment, as defined above, when administered to a mammal in need of such treatment. The therapeutically effective

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amount will vary depending upon the subject and disease condition being treated, the weight and age of the subject, the severity of the disease condition, the manner of administration and the like, which can readily be determined by one of ordinary skill in the art.

5           The term "linker," identified where appropriate by the symbol "X", refers to a group or groups that covalently link(s) from 2 to 10 ligands (as identified above) in a manner that provides for a compound capable of multi-valency when in the presence of at least one cellular receptor having 2 or more ligand binding sites. The linker is a ligand-orienting entity which may be chiral or achiral that permits  
10 attachment of multiple copies of a ligand (which may be the same or different) thereto. In some cases the linker may be biologically active. The term linker does not, however, extend to cover solid inert supports such as beads, glass particles, fibers and the like. But it is to be understood that the multi-binding compounds of this invention can be attached to a solid support if desired, for example, for use in  
15 separation and purification processes and for similar applications.

          The ligands and linkers which comprise the multibinding agents of the invention and the multibinding compounds themselves may have various stereoisomeric forms, including enantiomers and diastereomers. It is to be understood that the invention contemplates all possible stereoisomeric forms of  
20 multibinding compounds, and mixtures thereof.

          The extent to which multivalent binding is realized depends upon the efficiency with which the linker or linkers that joins the ligands presents them to their ligand binding sites on one or more receptors. Beyond presenting ligands for multivalent interactions with ligand binding sites, the linker spatially constrains  
25 these interactions to occur within dimensions defined by the linker. Thus the structural features of the linker (valency, geometry, orientation, size, flexibility,

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chemical composition) are features of multivalent compounds that play an important role in determining their activities.

### Methodology

5       The linker, when covalently attached to the ligands, provides a biocompatible, substantially non-immunogenic multi-binding compound of this invention. The biological activity of the multi-binding compound is highly sensitive to the valency, geometry, composition, size, flexibility or rigidity, etc. of the linker as well as the presence or absence of anionic or cationic charge, the relative hydrophobicity/hydrophilicity of the linker, and the like on the linker. In  
10       general, the linker may be chosen from any organic molecule construct that orients two or more ligands to the receptors to permit multi-valency. In this regard, the linker can be considered as a "framework" on which the ligands are arranged in order to bring about the desired ligand-orienting result, and thus produce a multi-binding compound.

15       Ancillary groups which enhance the water solubility/hydrophilicity of the linker and, accordingly, the resulting multi-binding compounds are useful in practicing this invention. Thus, it is within the scope of the present invention to use ancillary groups such as, for example, poly(ethylene glycols), alcohols, polyols, (e.g., glycerin, glycerol propoxylate, saccharides, including mono-,  
20       oligo- and polysaccharides, etc.) carboxylates, polycarboxylates, (e.g., polyglutamic acid, polyacrylic acid, etc.), amines, polyamines, (e.g., polylysine, poly(ethyleneimine), and the like) to enhance the water solubility and/or hydrophilicity of the multi-binding compounds of this invention. In preferred  
embodiments, the ancillary group used to improve water solubility/hydrophilicity  
25       will be a polyether. In particularly preferred embodiments, the ancillary group will be a poly(ethylene glycol).

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The incorporation of lipophilic ancillary groups within the structure of the linker to enhance the lipophilicity and/or hydrophobicity of the multi-binding compounds described herein is within the scope of this invention. Lipophilic groups useful with the linkers of this invention include, by way of example only, aryl and heteroaryl groups which, as above, may be either unsubstituted or substituted with other groups, but are at least substituted with a group which allows their covalent attachment to the linker. Other lipophilic groups useful with the linkers of this invention include fatty acid derivatives which do not form bilayers in aqueous medium until higher concentrations are reached.

Also within the scope of this invention is the use of ancillary groups which result in the multi-binding compound being incorporated into a vesicle such as a liposome or a micelle. The term "lipid" refers to any fatty acid derivative that is capable of forming a bilayer such that a hydrophobic portion of the lipid material orients toward the bilayer while a hydrophilic portion orients toward the aqueous phase. Hydrophilic characteristics derive from the presence of phosphato, carboxylic, sulfato, amino, sulfhydryl, nitro and other like groups well known in the art. Hydrophobicity could be conferred by the inclusion of groups that include, but are not limited to, long chain saturated and unsaturated aliphatic hydrocarbon groups of up to 20 carbon atoms and such groups substituted by one or more aryl, heteroaryl, cycloalkyl, and/or heterocyclic group(s). Preferred lipids are phosphoglycerides and sphingolipids, representative examples of which include phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, phosphatidic acid, palmitoyleoyl phosphatidylcholine, lysophosphatidylcholine, lysophosphatidyl-ethanolamine, dipalmitoylphosphatidylcholine, dioleoylphosphatidylcholine, distearoyl-phosphatidylcholine or dilinoleoylphosphatidylcholine could be used. Other compounds lacking phosphorus, such as sphingolipid and glycosphingolipid families are also within the group designated as lipid. Additionally, the

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amphipathic lipids described above may be mixed with other lipids including triglycerides and sterols.

The flexibility of the linker can be manipulated by the inclusion of ancillary groups which are bulky and/or rigid. The presence of bulky or rigid groups can hinder free rotation about bonds in the linker or bonds between the linker and the ancillary group(s) or bonds between the linker and the functional groups. Rigid groups can include, for example, those groups whose conformational lability is restrained by the presence of rings and/or multiple bonds, for example, aryl, heteroaryl, cycloalkyl and heterocyclic groups. Other groups which can impart rigidity include polypeptide groups such as oligo- or polyproline chains.

Rigidity can also be imparted electrostatically. Thus, if the ancillary groups are either positively or negatively charged, the similarly charged ancillary groups will force the presenter linker into a configuration affording the maximum distance between each of the like charges. The energetic cost of bringing the like-charged groups closer to each other will tend to hold the linker in a configuration that maintains the separation between the like-charged ancillary groups. Further ancillary groups bearing opposite charges will tend to be attracted to their oppositely charged counterparts and potentially may enter into both inter- and intramolecular ionic bonds. This non-covalent mechanism will tend to hold the linker into a conformation which allows bonding between the oppositely charged groups. The addition of ancillary groups which are charged, or alternatively, bear a latent charge when deprotected, following the addition to the linker, include deprotection of a carboxyl, hydroxyl, thiol or amino protecting group, by a change in pH, oxidation, reduction or other mechanisms known to those skilled in the art, is within the scope of this invention.



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Bulky groups can include, for example, large atoms, ions (e.g., iodine, sulfur, metal ions, etc.) or groups containing large atoms, polycyclic groups, including aromatic groups, non-aromatic groups and structures incorporating one or more carbon-carbon multiple bonds (i.e., alkenes and alkynes). Bulky groups  
5 can also include oligomers and polymers which are branched- or straight-chain species. Species that are branched are expected to increase the rigidity of the structure more per unit molecular weight gain than are straight-chain species.

In preferred embodiments, rigidity is imparted by the presence of cyclic groups (e.g., aryl, heteroaryl, cycloalkyl, heterocyclic, etc.). In still further  
10 preferred embodiments, the ring is an aryl group such as, for example, phenyl or naphthyl. In other preferred embodiments, the linker comprises one or more six-membered rings or crown groups which, while not rigid, retain the conformation of the linker through conformational entropy.

In view of the above, it is apparent that the appropriate selection of a linker  
15 group providing suitable orientation, entropy and physico-chemical properties is well within the skill of the art. Eliminating or reducing antigenicity of the multi-binding compounds described herein is also within the scope of this invention.

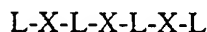
As explained above, the multi-binding compounds described herein  
20 comprise 2-10 ligands for the NMDA receptor attached to a linker that links the ligands in such a manner that they are presented to the NMDA receptor complex for multivalent interactions. The linker spatially constrains these interactions to occur within dimensions defined by the linker, thus greatly increasing biological activity of the multi-binding compound as compared to the same number of ligands used in mono-binding form.

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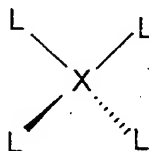
The multi-binding compounds of this invention are preferably represented by the empirical formula  $(L)_p(X)_q$  where L, X,  $p$  and  $q$  are as defined above. This is intended to include the several ways in which the ligands can be linked together in order to achieve the objective of multi-valency, and a more detailed explanation is described below.

As noted previously, the linker may be considered as a framework to which ligands are attached. Thus, it should be recognized that the ligands can be attached at any suitable position on this framework, for example, at the termini of a linear chain or at any intermediate position.

The simplest and most preferred multi-binding compound is a bivalent compound which can be represented as L-X-L, where L is a ligand and is the same or different and X is the linker. A trivalent compound could also be represented in a linear fashion, i.e., as a sequence of repeated units L-X-L-X-L, in which L is a ligand and is the same or different at each occurrence, as can X. However, a trimer can also be a multi-binding compound comprising three ligands attached to a central core, and thus represented as  $(L)_3X$ , where the linker X could include, for example, an aryl or cycloalkyl group. Tetravalent compounds can be represented as, for example, in a linear array:



or in a tetrahedral array:

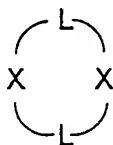


where X and L are as defined herein.

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The same considerations apply to higher multibinding compounds of this invention containing 5-10 ligands. However, for multibinding agents attached to a central linker such as aryl or cycloalkyl, there is a self-evident constraint that there must be sufficient attachment sites on the linker to accommodate the number of  
5 ligands present; for example, a benzene ring could not directly accommodate more than 6 ligands, whereas a multi-ring linker (e.g., biphenyl) could accommodate a larger number of ligands.

Certain of the above described compounds may alternatively be represented as cyclic chains of the form:



10 and variants thereof.

All of the above variations are intended to be within the scope of the invention defined by the formula  $(L)_p(X)_q$ .

In view of the above description of the linker, it is understood that the term "linker" when used in combination with the term "multibinding compound"  
15 includes both a covalently contiguous single linker (e.g., L-X-L) and multiple covalently non-contiguous linkers (L-X-L-X-L) within the multibinding compound.

#### Preparation of Multibinding Compounds

The multibinding compounds of this invention can be prepared from readily available starting materials using the following general methods and procedures. It  
20 will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are

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given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

5           Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. The choice of a suitable protecting group for a particular functional group as well as suitable conditions for protection and deprotection are well known in the art. For example, numerous protecting groups,  
10           and their introduction and removal, are described in T. W. Greene and G. M. Wuts, *Protecting Groups in Organic Synthesis*, Second Edition, Wiley, New York, 1991, and references cited therein.

          Any compound which acts as a ligand toward the NMDA receptor can be used as a ligand in this invention. It is desirable that the ligand or ligands be  
15           antagonists or partial agonists in order to modulate the activity of the NMDA receptor to lessen or alleviate conditions such as pain sensation, Alzheimer's, cognitive disorder, dementia, schizophrenia, ocular disease, AIDS-related complex, peripheral neuropathy, CV ischemia, infarction, stroke, motor neuron disease, epilepsy, seizure, convulsions, neurodegenerative disease, micturition  
20           disorders, migraine, Parkinson's disease, psychosis, Huntingdon's chorea and cardiac failure, wherein such compounds do not have the neurotoxic effects associated with current NMDA receptor noncompetitive binding compounds. In particular, a treatment for pain sensation is desirable as pain is a common effect associated with many of the above described conditions.

25           Of the many possible binding sites of the NMDA receptor, only a few are desirable for modulation of the receptor. As described in Kemp et al., Drugs

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Pharm. Sci. (1998) Vol. 89 (Receptor based Drug Design) pp. 297-321, many of the possible ligand-binding receptors have unwanted side effects. For example, ion channel blockers are too effective in that they have a high affinity for the cationic channel once it is opened, and have a low rate of reversibility. Therefore, once bound, the ion channel blocker is not easily removed, and therefore always blocks the receptor. This is known to cause behavioral, cardiovascular and cytotoxic effects. Similarly, antagonistic binding of the glutamate site would prevent all activity of the receptor. Bonding of a polyamine affects many different functions, including potassium transport, calcium transport, AMPA and the functioning of kinate receptors.

In contrast, antagonistic or partial agonist glycine ligands would modulate the activity of the receptor without entirely preventing the receptor from functioning, as glycine is known to act in a modulatory capacity. Also, as discussed elsewhere herein, subtype specific ligands would affect only certain NMDA receptors, leaving others to function, thereby alleviating some of the side effects currently known to occur with non-subtype specific NMDA receptor antagonists. Similar results may be seen with the use of redox site ligands.

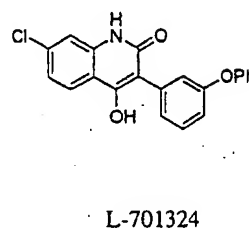
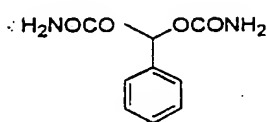
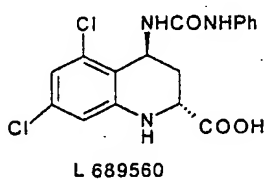
Therefore, ligands which are glycine antagonists or partial agonists or subtype specific antagonists or partial agonists are particularly desirable. As discussed in further detail below, numerous such ligands are known in the art and any of these known compounds or derivatives thereof may be employed as ligands in this invention. Such known ligands are now further described.

Many glycine antagonists, glycine partial agonists, glutamate antagonists, polyamines, ion channel blockers and redox site binders are known for binding to the NMDA receptor. Examples of such ligands are shown below, as well as other ligands which may fall into one or more of the above described categories.

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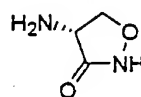
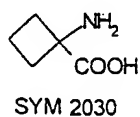
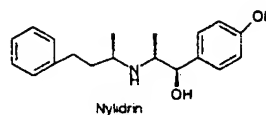
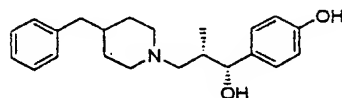
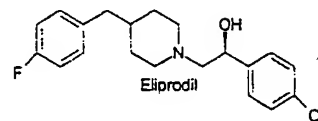
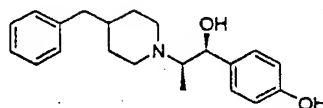
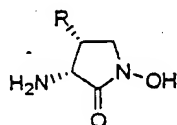
Ligands of the respective categories are referred to herein as ligands L-1 through L-7, wherein each of L-1, L-2, L-3, L-4, L-5, L-6 and L-7 represent a class of compounds, including derivatives thereof, as described above.

### Glycine Antagonists:



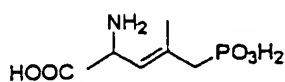
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### Glycine Partial Agonists:

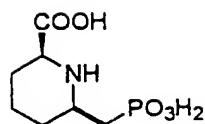


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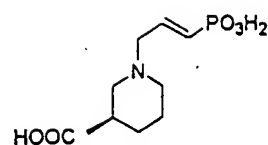
-48-

**Glutamate Antagonists:**

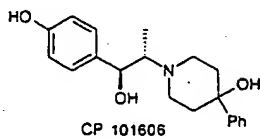
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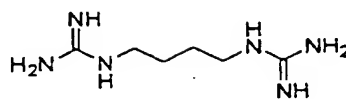
Selfotel



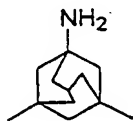
SDZ EAA 494

**Polyamines:**

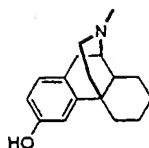
CP 101606



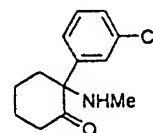
arcaine

**5 Ion Channel Blockers:**

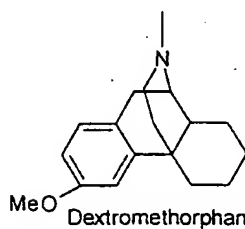
memantine



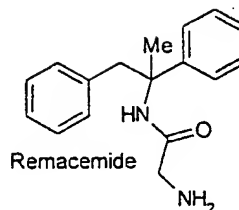
dextrorphan



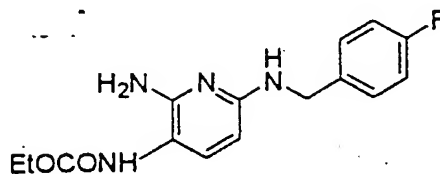
ketamine



Dextromethorphan



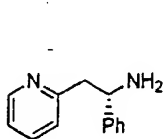
Remacemide

**Redox Ligands:**

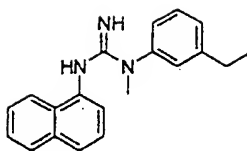
flupertine

-49-

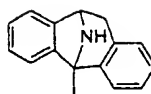
## Other Ligands:



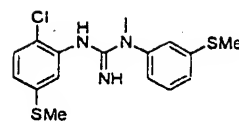
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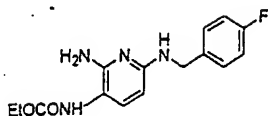
aptiganel



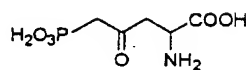
MK801



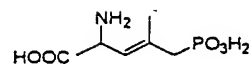
CNS-5161



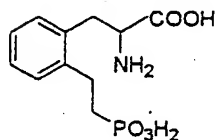
ketobemidone



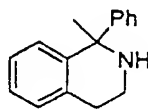
MDL 10043



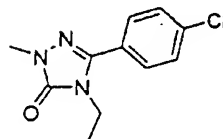
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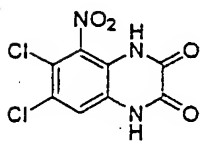
NPC 12626



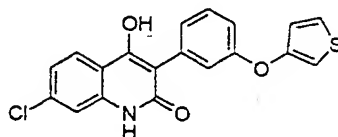
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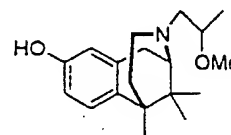
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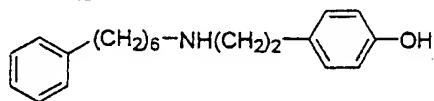
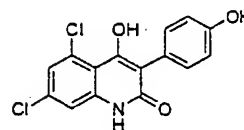
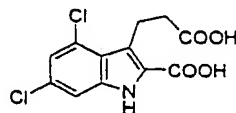
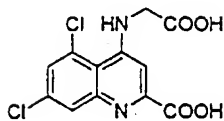
licostinel



L-705022



BIII 227Cl





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In particular, ligands of the above types L-1 through L-7 may comprise one or more of the following compounds: L-689560, felbamate, L-701324, HA 966, L-687414, ifenprodil, eliprodil, RO-25-6981, nylidrin, SYM 2030, cycloserine, CGP-37489, CP-101606, arcaine, memantidine, dextrophan, detromethorphan, remacemide, ketamine, ARL 15896AR, aptiganel, MK801, CNS-5161, selfotel, flupertine, SDZ EAA 494, ketobemidone, MDL 10043, CGP-40116, NPC 12626, FR 115427, MDL 27266, licostinel, L-705022, and BIII 227Cl. Other NMDA receptor ligands and derivatives may be known to those in the art. Preferentially, NMDA receptor ligands or derivatives thereof used in the invention are bound to only the NMDA receptor.

Further ligands which may be used in a compound of the invention as described herein may include, for example, other known NMDA receptor ligands such as dexanabinol, midafotel, RO-24-6173, RO-8-4304, GPI-3000, ADCI, FPL-16283, LY-274614, WAY-126090, HO-473, CNS-1531, CP-98113, ES-2421, CNS-1044, CNS-5065, CNS-1118, CNS-1524, CNS-1505, L-701315, L-701376, L-701252, L-698532, L-687414, L-701273, LY-235959, LY-233053, LY-235723, LY-233536, EMD-95885, CGP-39653, MRZ-2/579, CP-101616, AP-6, NC-1210, PD-158473, NPS-1506 and derivatives or analogs thereof.

The ligands may be bound together in any combination by a linker, as described herein. Therefor, any ligand capable of binding to an NMDA receptor, such as a glycine antagonist, glycine partial agonist, glutamate antagonist, polyamine, ion channel blocker or redox site binder may be combined with one or more glycine antagonist, glycine partial agonist, glutamate antagonist, polyamine, ion channel blocker or redox site binder to form a compound of the invention. For example, a glycine antagonist ligand may be joined by one or more linkers to one or more ligands selected from a glycine antagonist, glycine partial agonist, glutamate antagonist, polyamine, ion channel blocker and redox site binder. A

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glycine partial agonist may be joined by one or more linkers to one or more ligands selected from a glycine antagonist, glycine partial agonist, glutamate antagonist, polyamine, ion channel blocker and redox site binder. A glutamate antagonist may be joined by one or more linkers to one or more ligands selected from a glycine antagonist, glycine partial agonist, glutamate antagonist, polyamine, ion channel blocker and redox site binder. A polyamine may be joined by one or more linkers to one or more ligands selected from a glycine antagonist, glycine partial agonist, glutamate antagonist, polyamine, ion channel blocker and redox site binder. An ion channel blocker may be joined by one or more linkers to one or more ligands selected from a glycine antagonist, glycine partial agonist, glutamate antagonist, polyamine, ion channel blocker and redox site binder. A redox site binder may be joined by one or more linkers to one or more ligands selected from a glycine antagonist, glycine partial agonist, glutamate antagonist, polyamine, ion channel blocker and redox site binder. Other NMDA antagonists, partial agonists or agonists as known in the art may also be bound by one or more linkers to one or more ligands selected from a glycine antagonist, glycine partial agonist, glutamate antagonist, polyamine, ion channel blocker and redox site binder.

#### Combinatorial Libraries

Combinatorial approaches for identifying multimeric compounds which possess multibinding properties will now be discussed.

Specifically, factors such as the proper juxtaposition of the individual ligands of a multibinding compound with respect to the relevant array of binding sites on a target or targets is important in optimizing the interaction of the multibinding compound with its target(s) and to maximize the biological advantage through multivalency. One approach is to identify a library of candidate multibinding compounds with properties spanning the multibinding parameters that

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are relevant for a particular target. These parameters include: (1) the identity of ligand(s), (2) the orientation of ligands, (3) the valency of the construct, (4) linker length, (5) linker geometry, (6) linker physical properties, and (7) linker chemical functional groups.

- 5 Libraries of multimeric compounds potentially possessing multibinding properties (i.e., candidate multibinding compounds) and comprising a multiplicity of such variables are prepared and these libraries are then evaluated via conventional assays corresponding to the ligand selected and the multibinding parameters desired. Considerations relevant to each of these variables are set  
10 forth below.

#### Selection of ligand(s)

- A single ligand or set of ligands is (are) selected for incorporation into the libraries of candidate multibinding compounds which library is directed against a particular biological target or targets. The only requirement for the ligands chosen  
15 is that they are capable of interacting with the selected target(s). Thus, ligands may be known drugs, modified forms of known drugs, substructures of known drugs or substrates of modified forms of known drugs (which are competent to interact with the target), or other compounds. Ligands are preferably chosen based on known favorable properties that may be projected to be carried over to or  
20 amplified in multibinding forms. Favorable properties include demonstrated safety and efficacy in human patients, ability to increase insulin sensitivity, ability to lower serum triglyceride, cholesterol and/or fatty acid levels, etc. However, it is crucial to note that ligands which display an unfavorable property from among the previous list may obtain a more favorable property through the process of  
25 multibinding compound formation; i.e., ligands should not necessarily be excluded on such a basis. For example, a ligand that is not sufficiently potent at a particular target so as to be efficacious in a human patient may become highly potent and

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efficacious when presented in multibinding form. A ligand that is potent and efficacious but not of utility because of a non-mechanism-related toxic side effect may have increased therapeutic index (increased potency relative to toxicity) as a multibinding compound. Compounds that exhibit short *in vivo* half-lives may have extended half-lives as multibinding compounds. Physical properties of ligands that limit their usefulness (e.g. poor bioavailability due to low solubility, hydrophobicity, hydrophilicity) may be rationally modulated in multibinding forms, providing compounds with physical properties consistent with the desired utility.

10    Orientation: selection of ligand attachment points and linking chemistry

Several points are chosen on each ligand at which to attach the ligand to the linker. The selected points on the ligand/linker for attachment are functionalized to contain complementary reactive functional groups. This permits probing the effects of presenting the ligands to their receptor(s) in multiple relative orientations, an important multibinding design parameter. The only requirement for choosing attachment points is that attaching to at least one of these points does not abrogate activity of the ligand. Such points for attachment can be identified by structural information when available. Alternatively, evaluation of ligand/target binding by nuclear magnetic resonance will permit the identification of sites non-essential for ligand/target binding. See, for example, Fesik, et al., U.S. Patent No. 5,891,643. When such structural information is not available, utilization of structure-activity relationships (SAR) for ligands will suggest positions where substantial structural variations are and are not allowed. In the absence of both structural and SAR information, a library is merely selected with multiple points of attachment to allow presentation of the ligand in multiple distinct orientations. Subsequent evaluation of this library will indicate what positions are suitable for attachment.

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It is important to emphasize that positions of attachment that do abrogate the activity of the monomeric ligand may also be advantageously included in candidate multibinding compounds in the library provided that such compounds bear at least one ligand attached in a manner which does not abrogate intrinsic activity. This selection derives from, for example, heterobivalent interactions within the context of a single target molecule. For example, consider a receptor antagonist ligand bound to its target receptor, and then consider modifying this ligand by attaching to it a second copy of the same ligand with a linker which allows the second ligand to interact with the same receptor molecule at sites proximal to the antagonist binding site, which include elements of the receptor that are not part of the formal antagonist binding site and/or elements of the matrix surrounding the receptor such as the membrane. Here, the most favorable orientation for interaction of the second ligand molecule with the receptor/matrix may be achieved by attaching it to the linker at a position which abrogates activity of the ligand at the formal antagonist binding site. Another way to consider this is that the SAR of individual ligands within the context of a multibinding structure is often different from the SAR of those same ligands in monomeric form.

The foregoing discussion focused on bivalent interactions of dimeric compounds bearing two copies of the same ligand joined to a single linker through different attachment points, one of which may abrogate the binding/activity of the monomeric ligand. It should also be understood that bivalent advantage may also be attained with heterodimeric constructs bearing two different ligands that bind to common or different targets. For example, a glycine antagonist and a polyamine site antagonist may be joined to a linker through attachment points which do not abrogate the binding affinity of the monomeric ligands for their respective receptor sites. The dimeric compound may achieve enhanced affinity for both receptors due to favorable interactions between the glycine ligand and elements proximal to the formal polyamine ligand binding site and between the polyamine ligand and

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elements proximal to the formal glycine ligand binding site. Thus, the dimeric compound may be a more potent and selective antagonist of the NMDA receptor and a superior therapy for pain.

5       Once the ligand attachment points have been chosen, one identifies the types of chemical linkages that are possible at those points. The most preferred types of chemical linkages are those that are compatible with the overall structure of the ligand (or protected forms of the ligand), readily and generally formed, stable and intrinsically innocuous under typical chemical and physiological conditions, and compatible with a large number of available linkers. Amide  
10       bonds, ethers, amines, carbamates, ureas, and sulfonamides are but a few examples of preferred linkages.

Linkers: spanning relevant multibinding parameters through selection of valency, linker length, linker geometry, rigidity, physical properties, and chemical functional groups

15       In the library of linkers employed to generate the library of candidate multibinding compounds, the selection of linkers employed in this library of linkers takes into consideration the following factors.

20       Valency. In most instances the library of linkers is initiated with divalent linkers. The choice of ligands and proper juxtaposition of two ligands relative to their binding sites permits such molecules to exhibit target binding affinities and specificities more than sufficient to confer biological advantage. Furthermore, divalent linkers or constructs are also typically of modest size such that they retain the desirable biodistribution properties of small molecules.

25       Linker length. Linkers are chosen in a range of lengths to allow the spanning of a range of inter-ligand distances that encompass the distance

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preferable for a given divalent interaction. In some instances the preferred distance can be estimated rather precisely from high-resolution structural information of targets, typically enzymes and soluble receptor targets. In other instances where high-resolution structural information is not available, one can

5 make use of simple models to estimate the maximum distance between binding sites either on adjacent receptors or at different locations on the same receptor. In situations where two binding sites are present on the same target (or target subunit for multisubunit targets), preferred linker distances are 2-20 Å, with more preferred linker distances of 3-12 Å. In situations where two binding sites reside

10 on separate (e.g., protein) target sites, preferred linker distances are 20-100 Å, with more preferred distances of 30-70 Å.

Linker geometry and rigidity. The combination of ligand attachment site, linker length, linker geometry, and linker rigidity determine the possible ways in which the ligands of candidate multibinding compounds may be displayed in three

15 dimensions and thereby presented to their binding sites. Linker geometry and rigidity are nominally determined by chemical composition and bonding pattern, which may be controlled and are systematically varied as another spanning function in a multibinding array. For example, linker geometry is varied by attaching two ligands to the ortho, meta, and para positions of a benzene ring, or

20 in *cis*- or *trans*-arrangements at the 1,1- vs. 1,2- vs. 1,3- vs. 1,4- positions around a cyclohexane core or in *cis*- or *trans*-arrangements at a point of ethylene unsaturation. Linker rigidity is varied by controlling the number and relative energies of different conformational states possible for the linker. For example, a divalent compound bearing two ligands joined by 1,8-octyl linker has many more

25 degrees of freedom, and is therefore less rigid than a compound in which the two ligands are attached to the 4,4' positions of a biphenyl linker.

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Linker physical properties. The physical properties of linkers are nominally determined by the chemical constitution and bonding patterns of the linker, and linker physical properties impact the overall physical properties of the candidate multibinding compounds in which they are included. A range of linker compositions is typically selected to provide a range of physical properties (hydrophobicity, hydrophilicity, amphiphilicity, polarization, acidity, and basicity) in the candidate multibinding compounds. The particular choice of linker physical properties is made within the context of the physical properties of the ligands they join and, preferably, the goal is to generate molecules with favorable properties.

For example, linkers can be selected to avoid those that are too hydrophilic or too hydrophobic to be readily absorbed and/or distributed *in vivo*.

Linker chemical functional groups. Linker chemical functional groups are selected to be compatible with the chemistry chosen to connect linkers to the ligands and to impart the range of physical properties sufficient to span initial examination of this parameter.

#### Combinatorial synthesis

Having chosen a set of  $n$  ligands ( $n$  being determined by the sum of the number of different attachment points for each ligand chosen) and  $m$  linkers by the process outlined above, a library of  $(n!)m$  candidate divalent multibinding compounds is prepared which spans the relevant multibinding design parameters for a particular target. For example, an array generated from two ligands, one which has two attachment points (A1, A2) and one which has three attachment points (B1, B2, B3) joined in all possible combinations provide for at least 15 possible combinations of multibinding compounds:

A1-A1	A1-A2	A1-B1	A1-B2	A1-B3	A2-A2	A2-B1	A2-B2
A2-B3	B1-B1	B1-B2	B1-B3	B2-B2	B2-B3	B3-B3	



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When each of these combinations is joined by 10 different linkers, a library of 150 candidate multibinding compounds results.

Given the combinatorial nature of the library, common chemistries are preferably used to join the reactive functionalities on the ligands with complementary reactive functionalities on the linkers. The library therefore lends itself to efficient parallel synthetic methods. The combinatorial library can employ solid phase chemistries well known in the art wherein the ligand and/or linker is attached to a solid support. Alternatively and preferably, the combinatorial library is prepared in the solution phase. After synthesis, candidate multibinding compounds are optionally purified before assaying for activity by, for example, chromatographic methods (e.g., HPLC).

Analysis of array by biochemical, analytical, pharmacological, and computational methods

Various methods are used to characterize the properties and activities of the candidate multibinding compounds in the library to determine which compounds possess multibinding properties. Physical constants such as solubility under various solvent conditions and logD/clogD values are determined. A combination of NMR spectroscopy and computational methods is used to determine low-energy conformations of the candidate multibinding compounds in fluid media. The ability of the members of the library to bind to the desired target and other targets is determined by various standard methods, which include radioligand displacement assays for receptor and ion channel targets, and kinetic inhibition analysis for many enzyme targets. *In vitro* efficacy, such as for receptor agonists and antagonists, ion channel blockers, and antimicrobial activity are also determined. Pharmacological data, including oral absorption, everted gut penetration, other pharmacokinetic parameters and efficacy data are determined in

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appropriate models. In this way, key structure-activity relationships are obtained for multibinding design parameters which are then used to direct future work.

The members of the library which exhibit multibinding properties, as defined herein, can be readily determined by conventional methods. First, those  
5 members which exhibit multibinding properties are identified by conventional methods as described above, including conventional assays (both *in vitro* and *in vivo*).

Second, ascertaining the structure of those compounds which exhibit multibinding properties can be accomplished via art recognized procedures. For  
10 example, each member of the library can be encrypted or tagged with appropriate information allowing determination of the structure of relevant members at a later time. See, for example, Dower, et al., International Patent Application Publication No. WO 93/06121; Brenner, et al., Proc. Natl. Acad. Sci., USA, 89:5181 (1992); Gallop, et al., U.S. Patent No. 5,846,839; each of which is  
15 incorporated herein by reference in its entirety. Alternatively, the structure of relevant multivalent compounds can also be determined from soluble and untagged libraries of candidate multivalent compounds by methods known in the art, such as those described by Hindsgaul, et al., Canadian Patent Application No. 2,240,325 which was published on July 11, 1998. Such methods couple frontal affinity  
20 chromatography with mass spectroscopy to determine both the structure and relative binding affinities of candidate multibinding compounds to receptors.

The process set forth above for dimeric candidate multibinding compounds can, of course, be extended to trimeric candidate compounds and higher analogs thereof.

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Follow-up synthesis and analysis of additional array(s)

Based on the information obtained through analysis of the initial library, an optional component of the process is to ascertain one or more promising multibinding "lead" compounds as defined by particular relative ligand orientations, linker lengths, linker geometries, etc. Additional libraries can then be generated around these leads to provide for further information regarding structure to activity relationships. These arrays typically bear more focused variations in linker structure to further optimize target affinity and/or activity at the target (antagonism, partial agonism, etc.), and/or alter physical properties. By iterative redesign/analysis using the novel principles of multibinding design along with classical medicinal chemistry, biochemistry, and pharmacology approaches, one is able to prepare and identify optimal multibinding compounds that exhibit biological advantage towards their targets and as therapeutic agents.

To further elaborate upon this procedure, suitable divalent linkers include, by way of example only, those derived from dicarboxylic acids, disulfonylhalides, dialdehydes, dipseudohalides, diketones, dihalides, diisocyanates, diamines, diols, diboronates, mixtures of carboxylic acids, sulfonylhalides, aldehydes, ketones, halides, isocyanates, amines and diols. In each case, the carboxylic acid, sulfonylhalide, aldehyde, ketone, halide, isocyanate, amine and diol functional group is reacted with a complementary functionality on the ligand to form a covalent linkage. Such complementary functionality is well known in the art as illustrated in the following table, which is exemplary only:

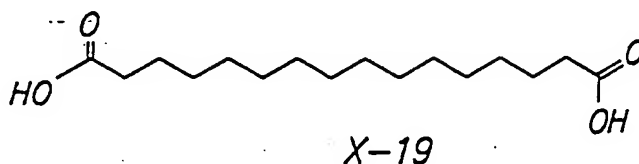
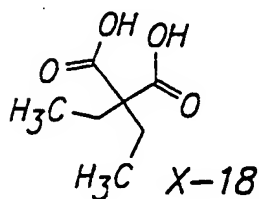
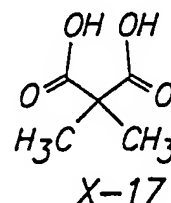
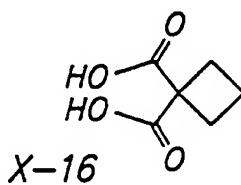
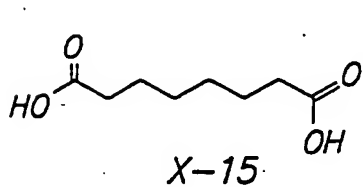
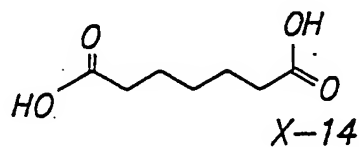
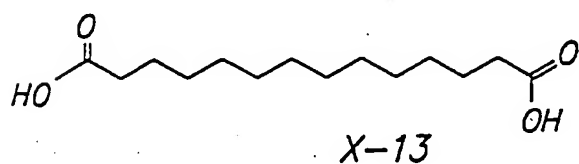
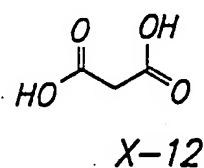
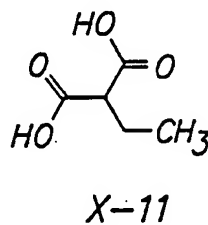
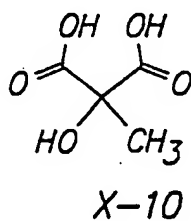
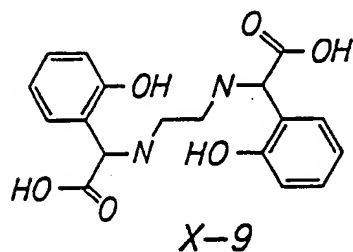
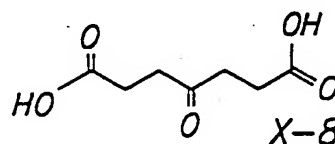
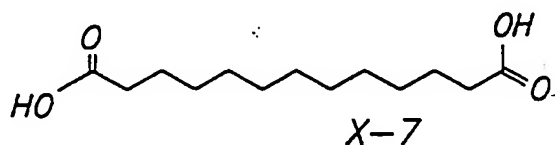
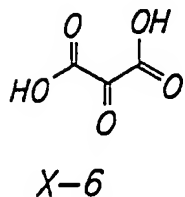
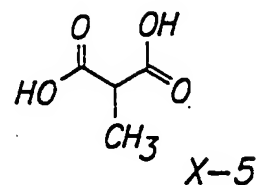
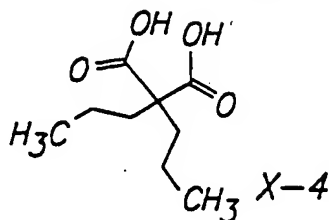
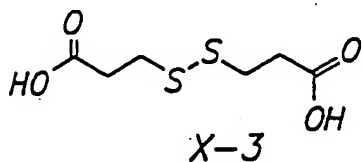
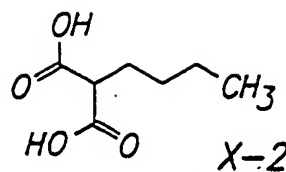
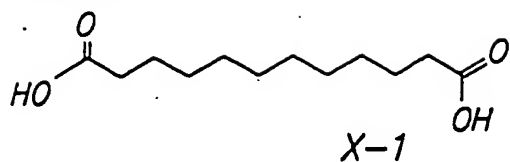
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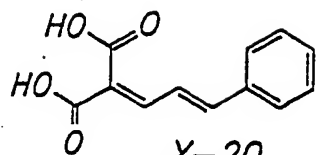
## COMPLEMENTARY BINDING CHEMISTRIES

	<u>First Reactive Group</u>	<u>Second Reactive Group</u>	<u>Linkage</u>
	hydroxyl	isocyanate	urethane
	amine	epoxide	$\beta$ -hydroxyamine
5	sulfonyl halide	amine	sulfonamide
	carboxyl acid	amine	amide
	hydroxyl	alkyl/aryl halide	ether
	aldehyde	amine/ $\text{NaCNBH}_3$	amine
	ketone	amine/ $\text{NaCNBH}_3$	amine
10	amine	isocyanate	urea

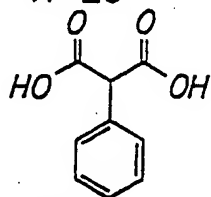
Exemplary linkers include the following linkers identified as X-1 through X-418 as set forth below in Table 1:

## Diacids

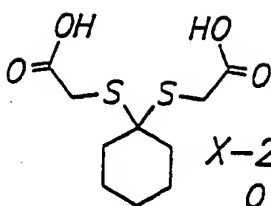




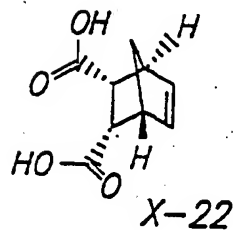
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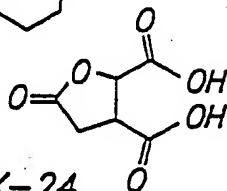
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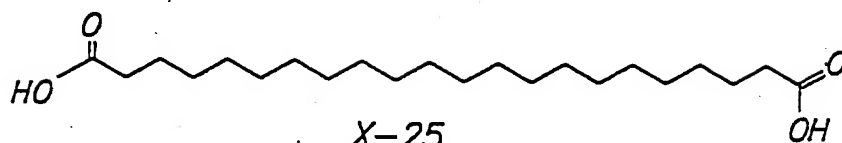
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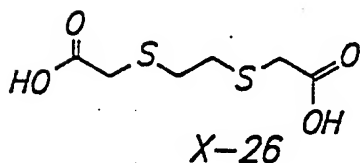
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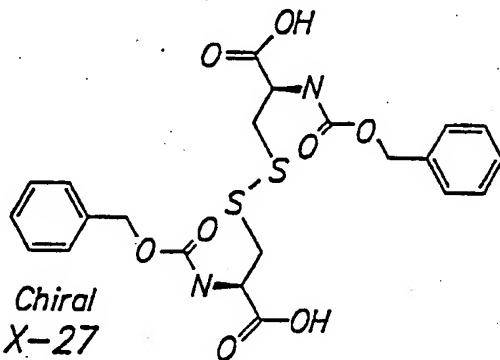
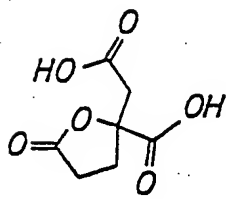
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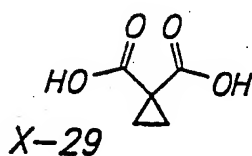
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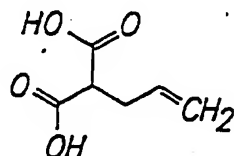
X-26

Chiral  
X-27

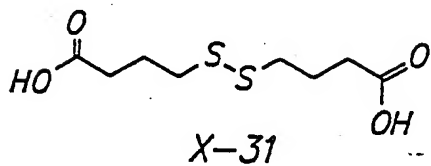
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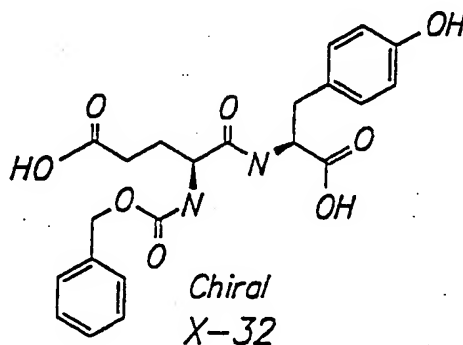
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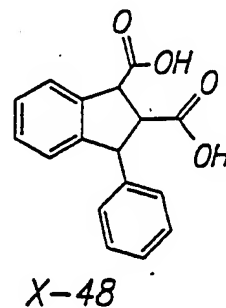
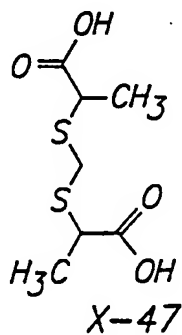
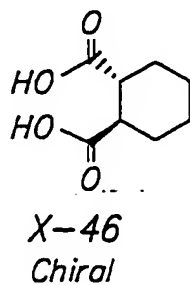
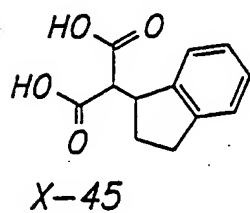
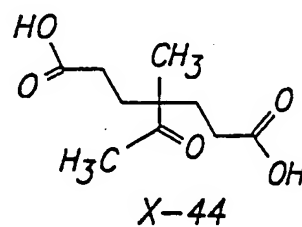
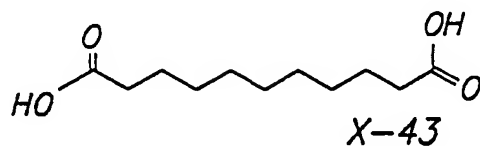
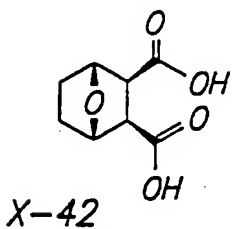
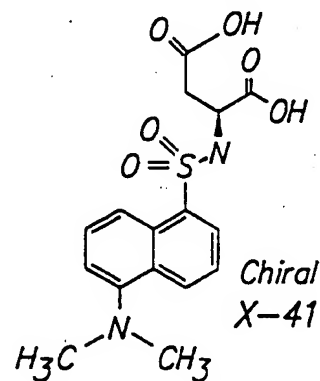
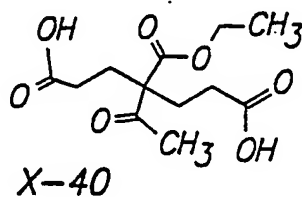
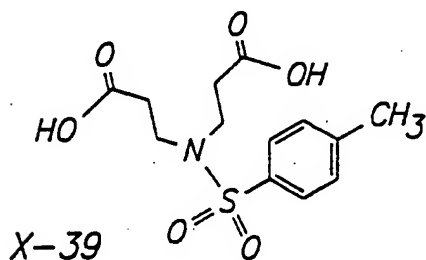
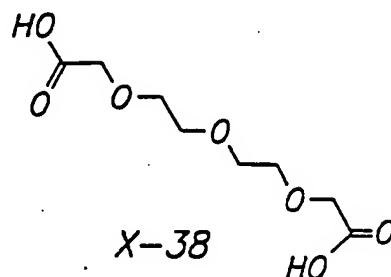
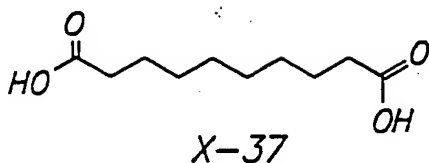
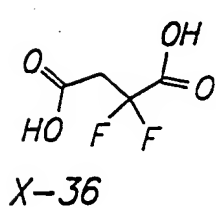
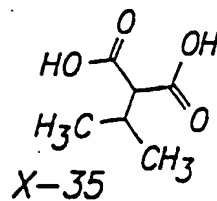
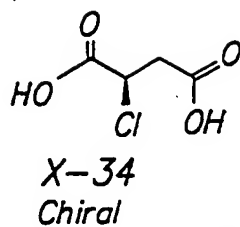


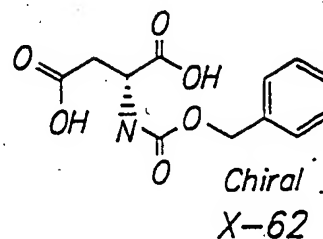
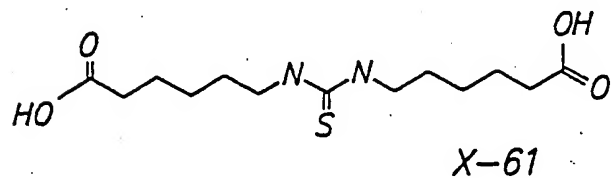
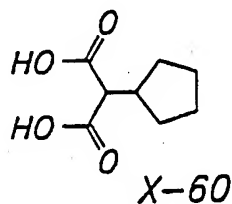
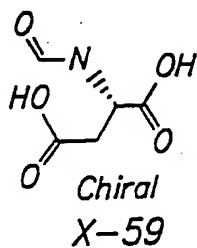
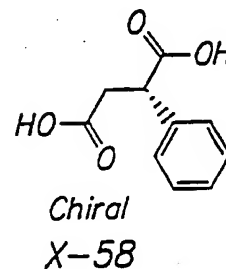
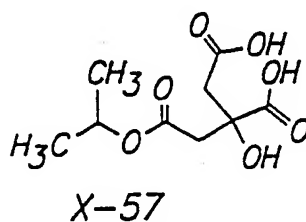
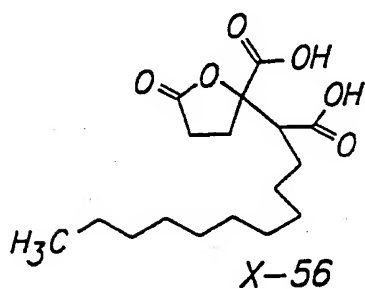
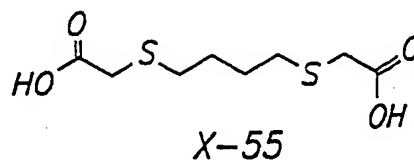
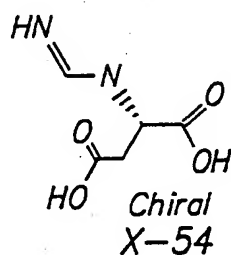
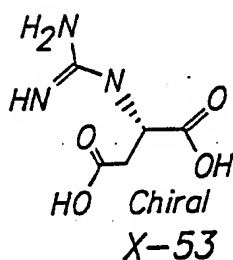
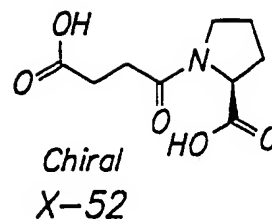
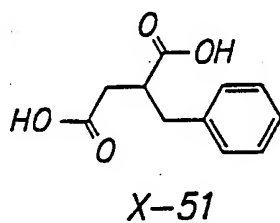
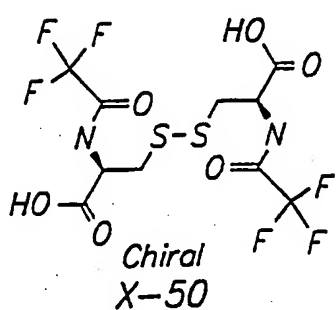
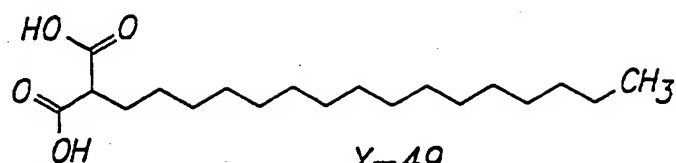
X-30



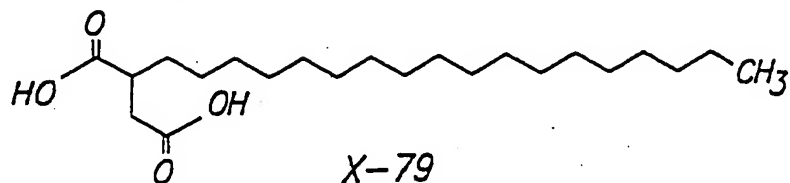
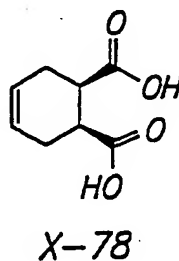
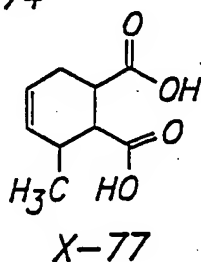
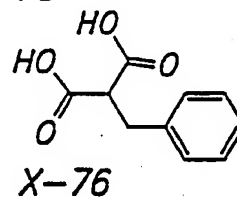
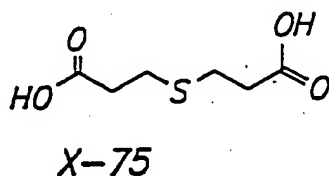
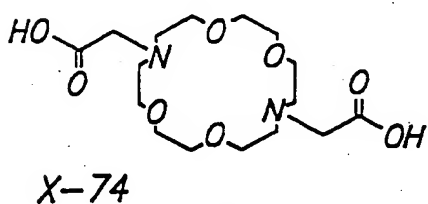
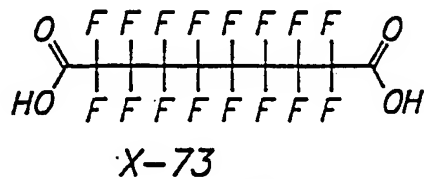
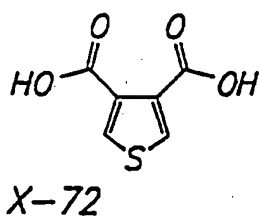
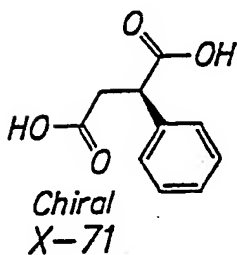
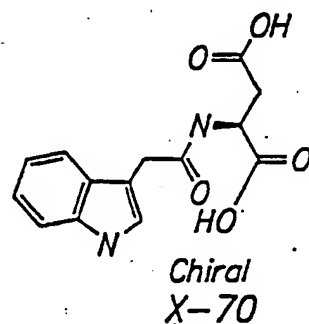
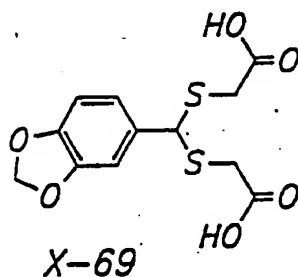
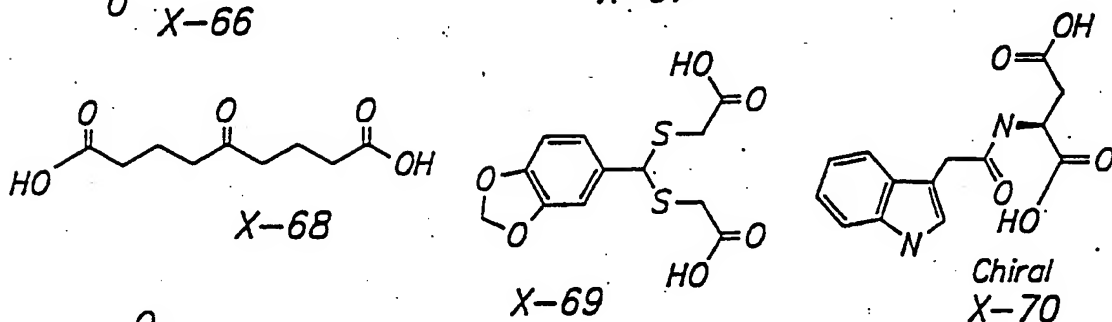
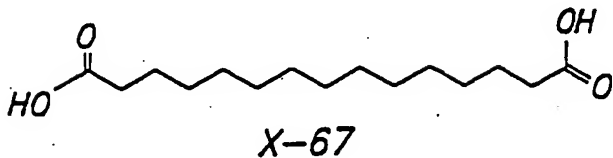
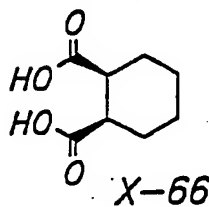
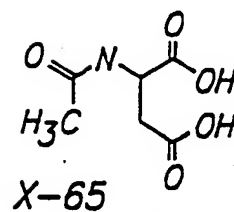
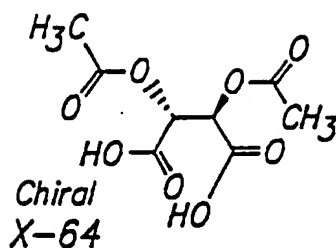
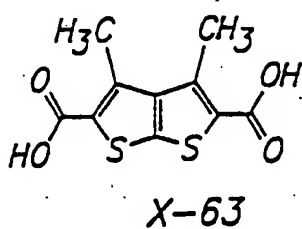
X-31

Chiral  
X-32

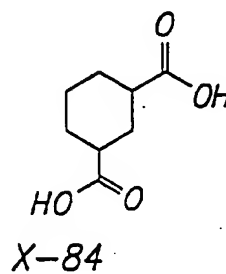
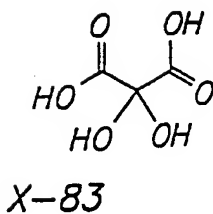
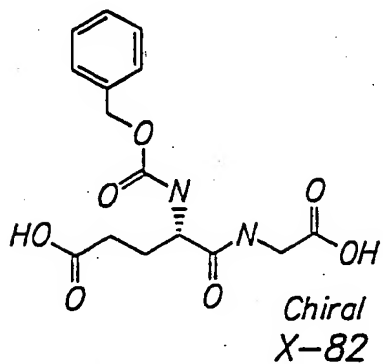
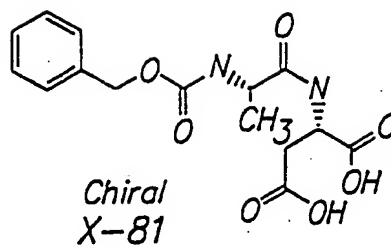
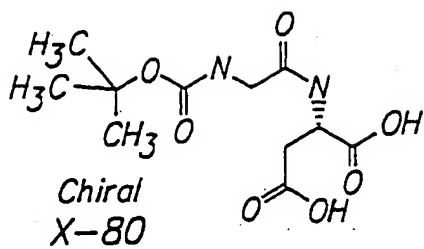


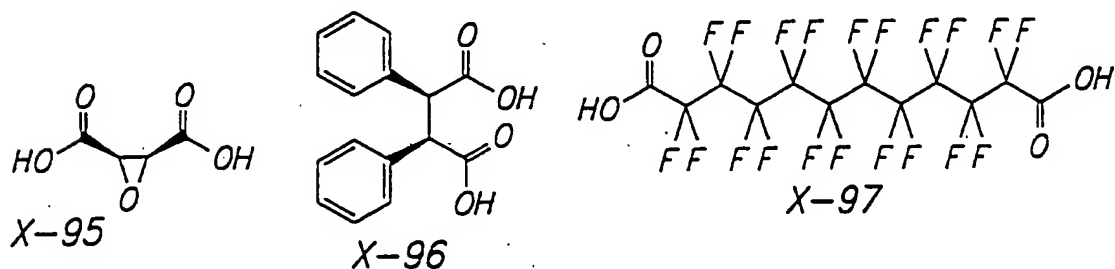
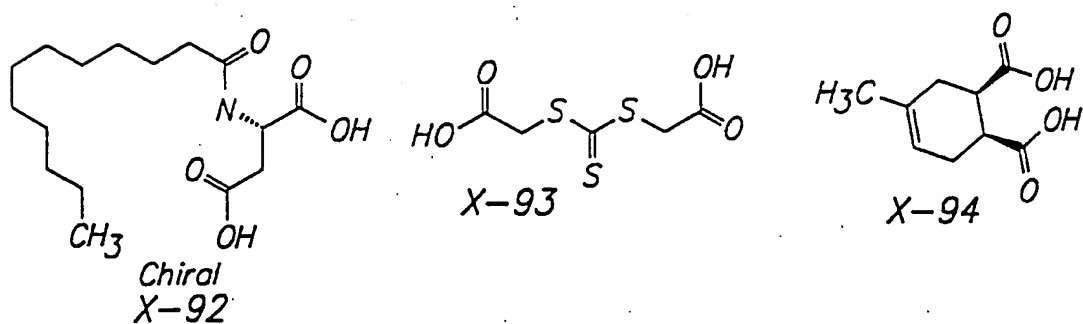
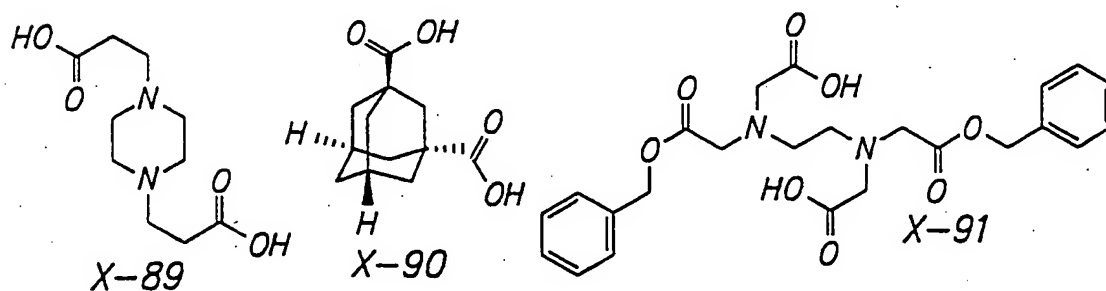
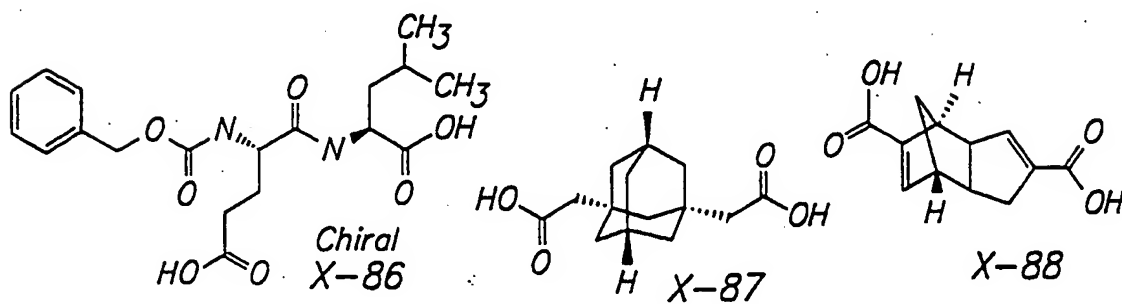




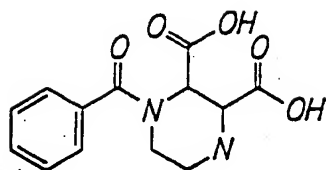


-67 (a)-

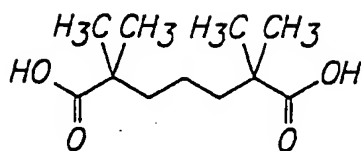




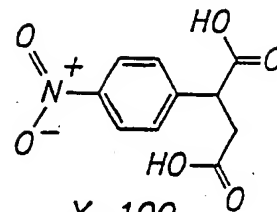
-67 (c)-



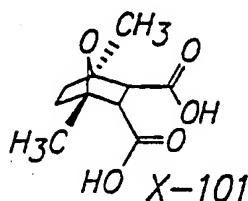
X-98



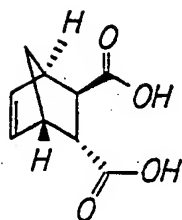
X-99



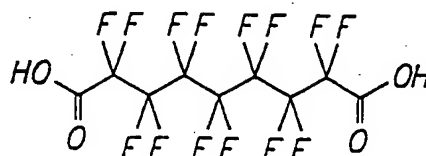
X-100



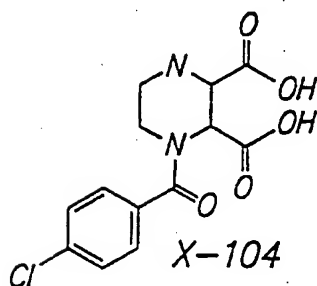
X-101



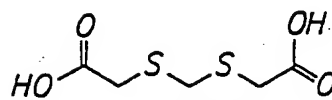
X-102



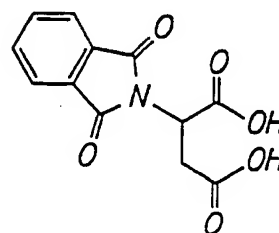
X-103



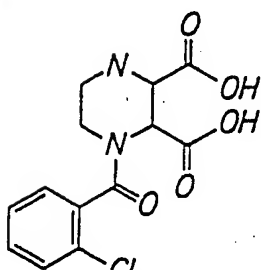
X-104



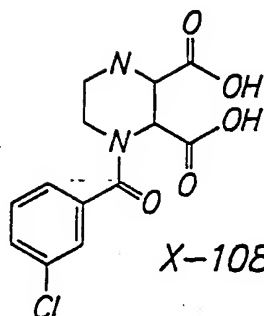
X-105



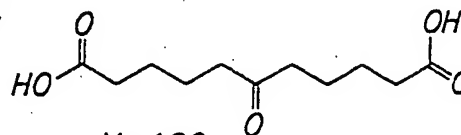
X-106



X-107

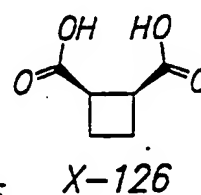
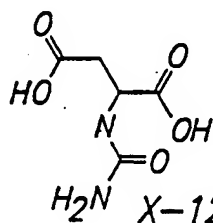
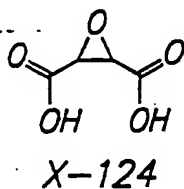
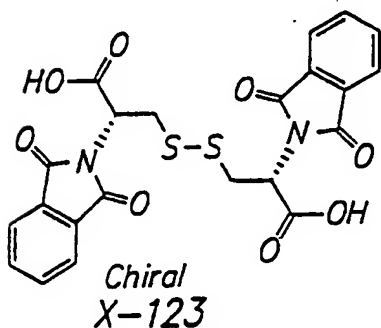
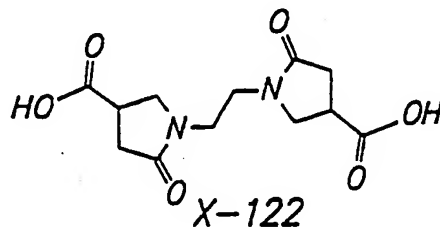
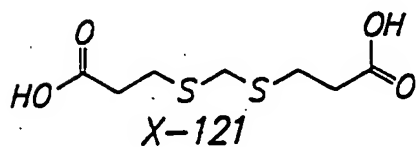
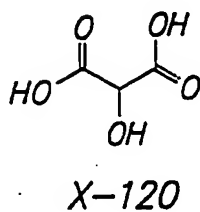
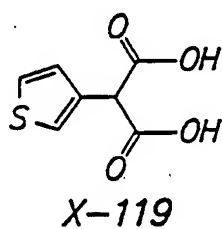
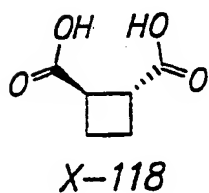
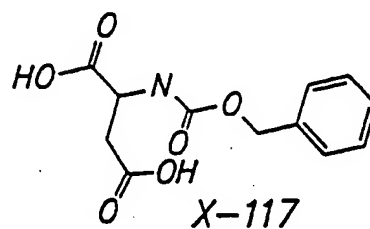
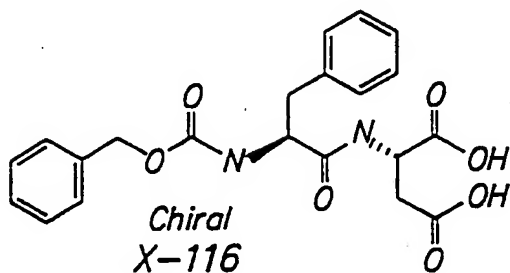
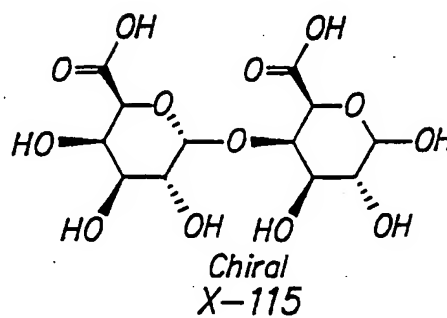
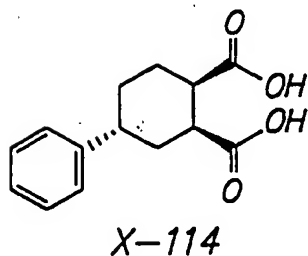
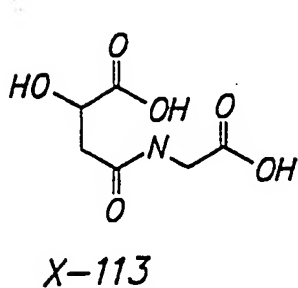
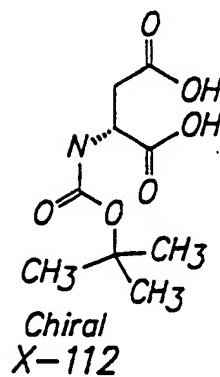
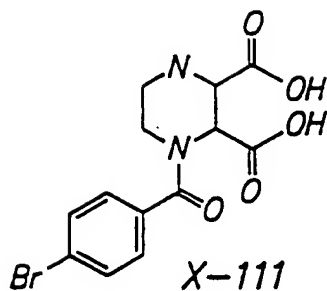
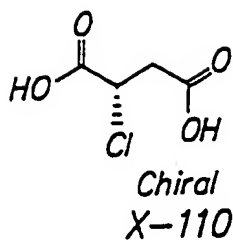


X-108

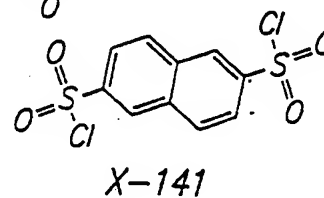
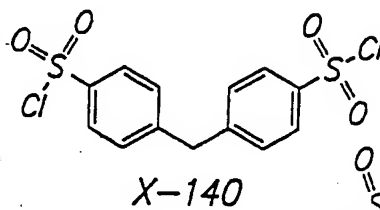
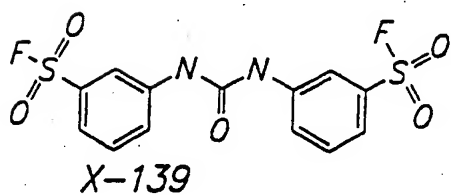
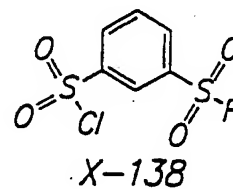
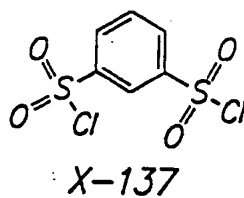
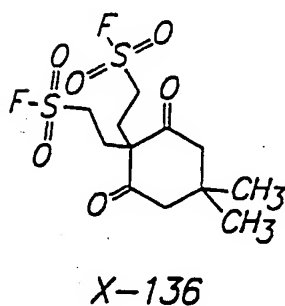
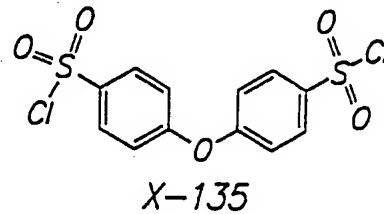
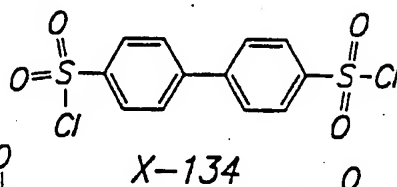
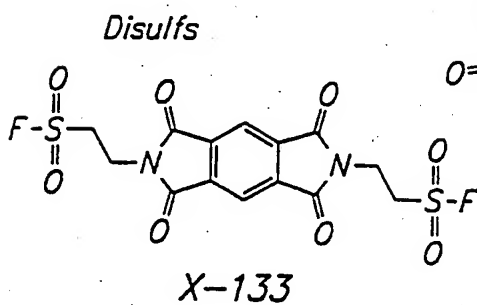
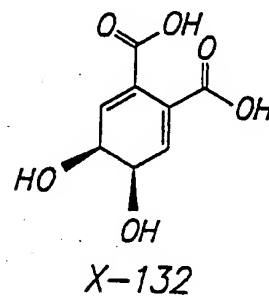
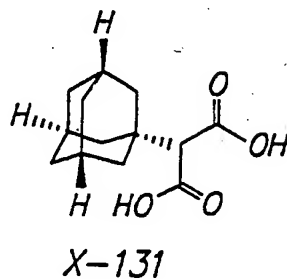
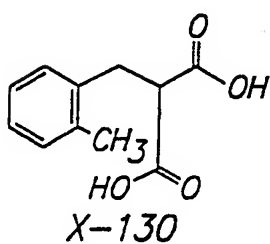
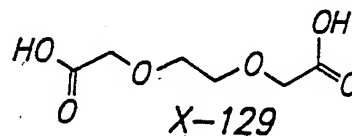
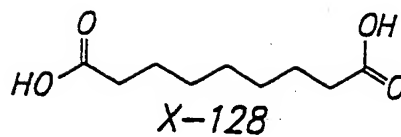
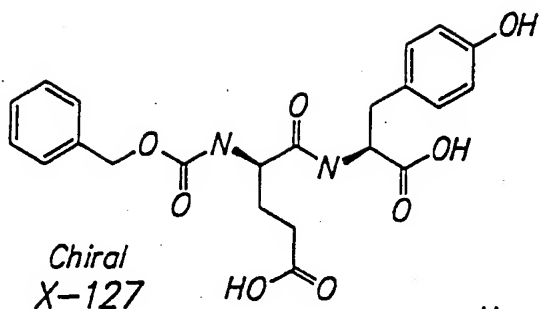


X-109

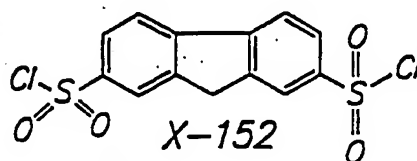
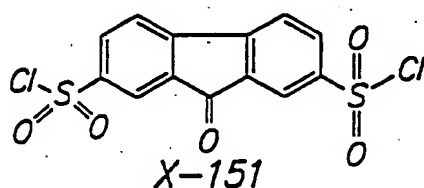
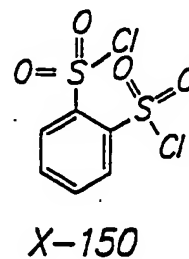
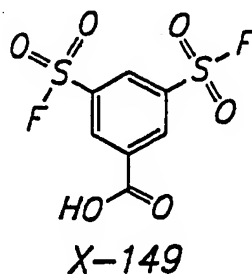
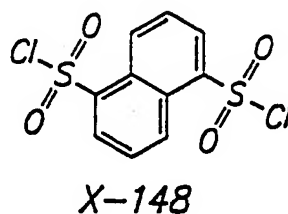
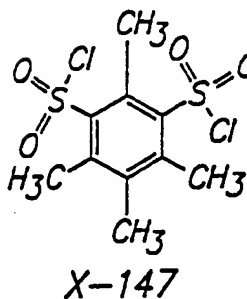
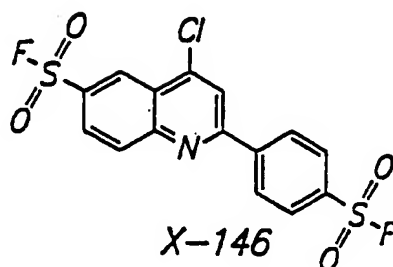
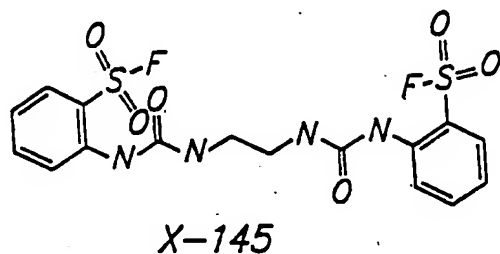
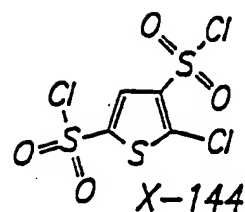
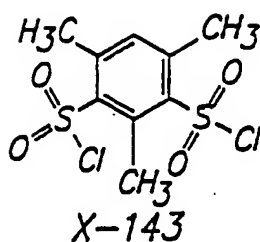
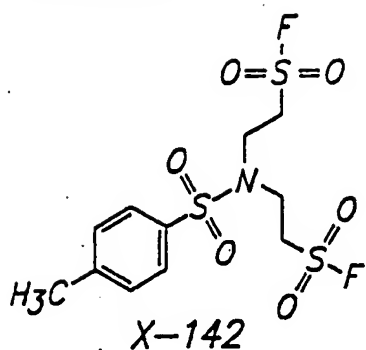
-67 (d)-



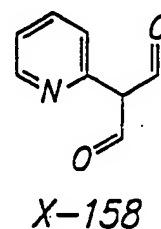
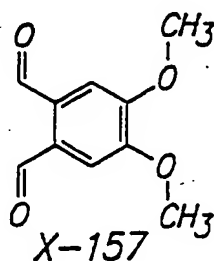
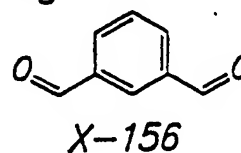
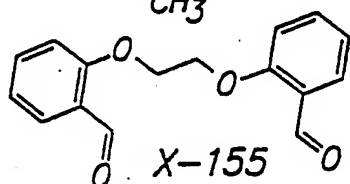
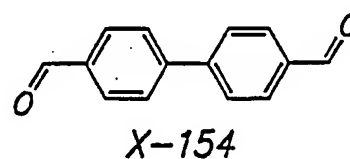
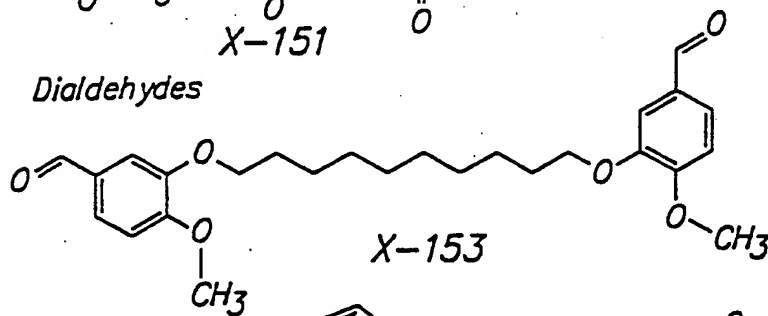
-67 (e)-



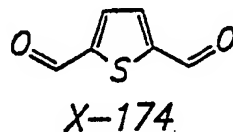
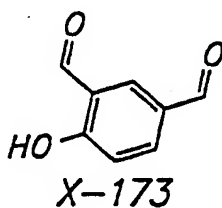
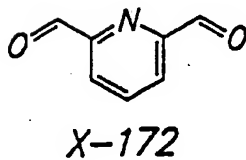
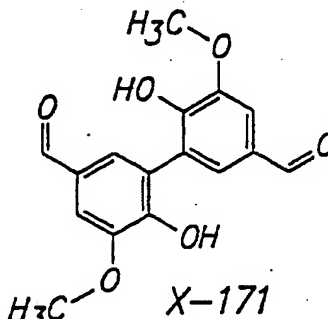
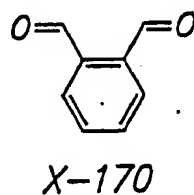
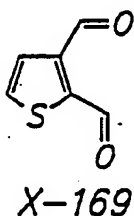
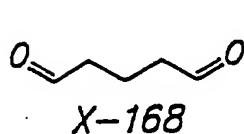
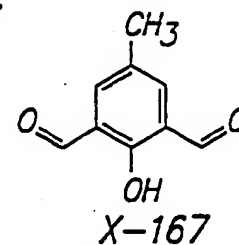
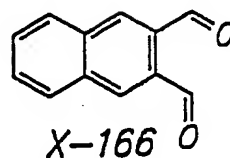
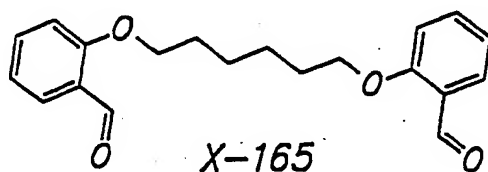
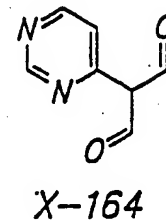
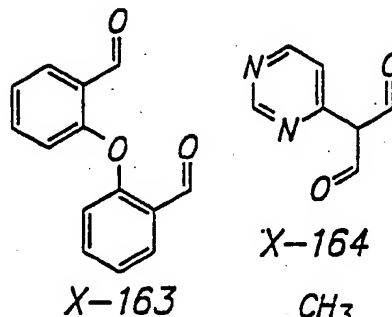
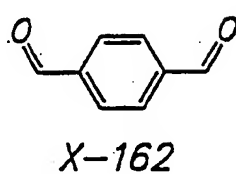
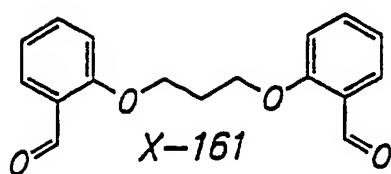
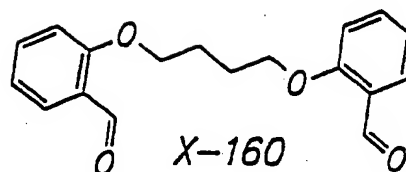
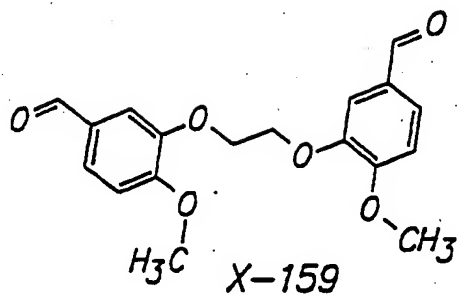
--67 (f)--



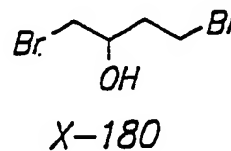
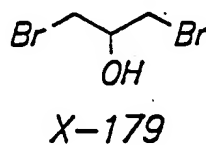
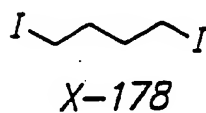
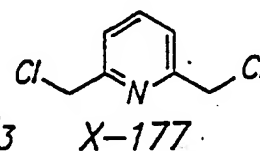
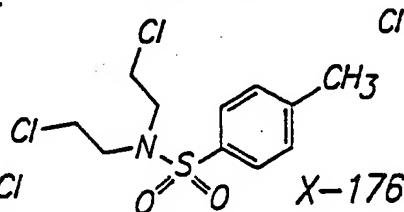
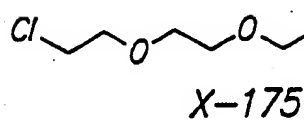
Dialdehydes



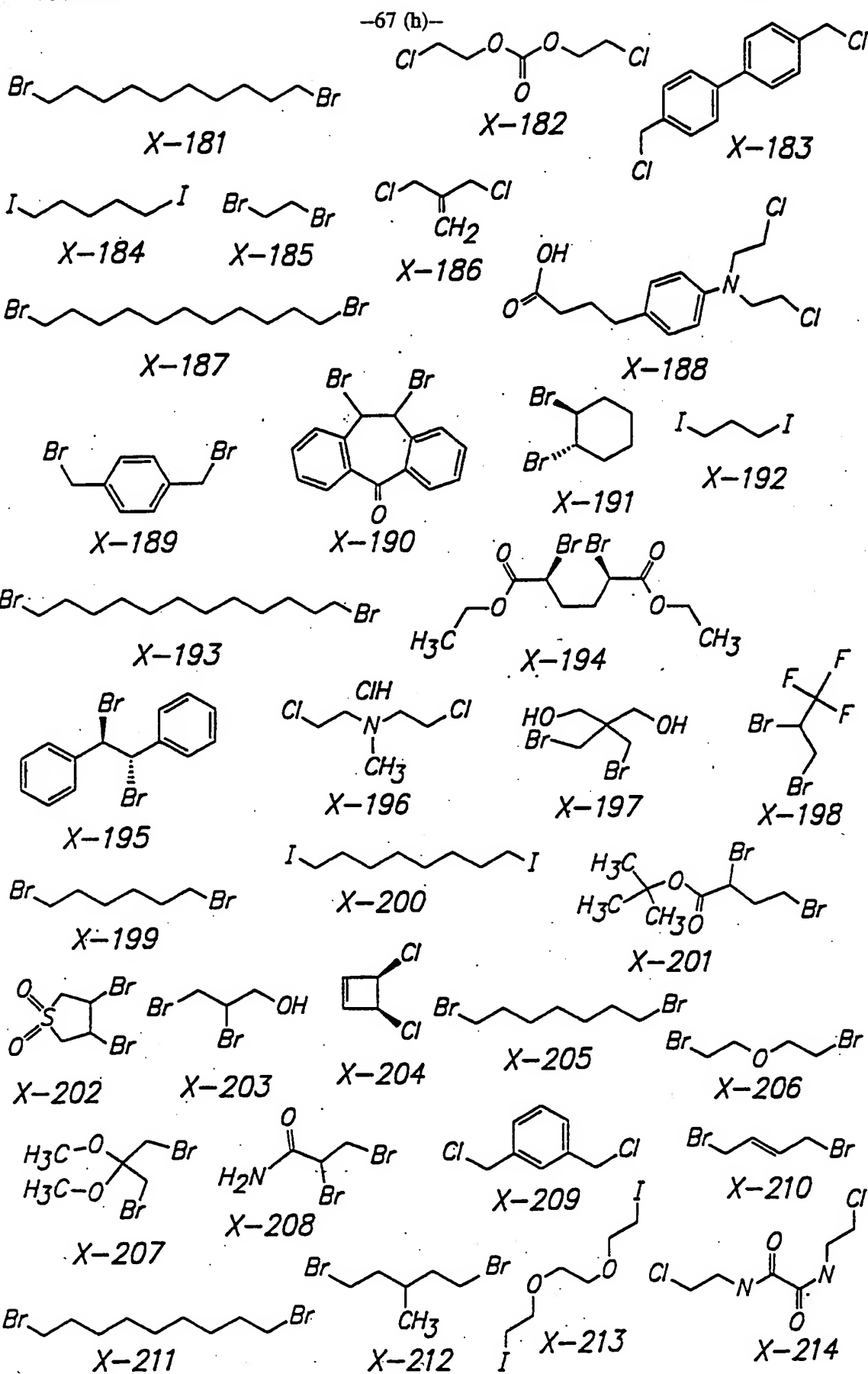
-67 (g)-



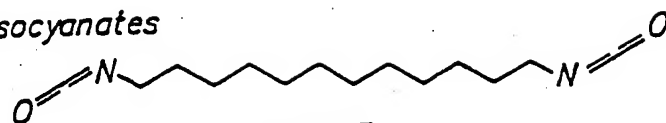
Dihalides



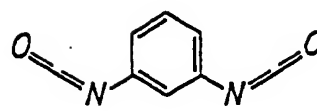




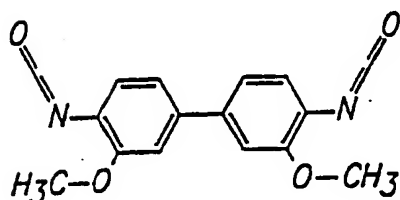
## Diisocyanates



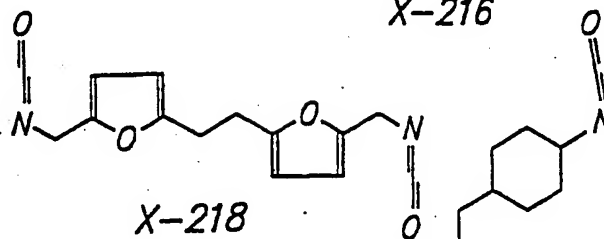
X-215



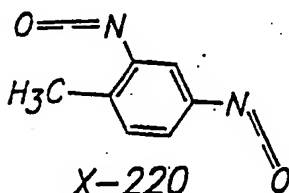
X-216



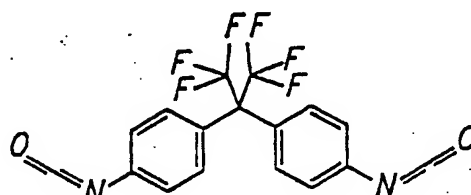
X-217



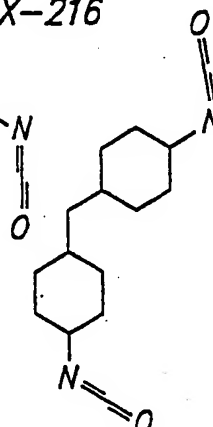
X-218



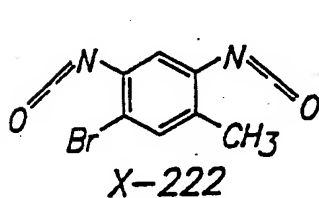
X-220



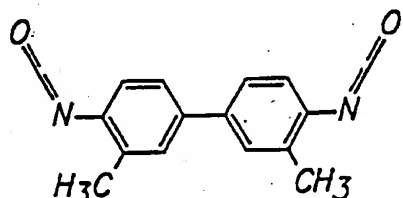
X-221



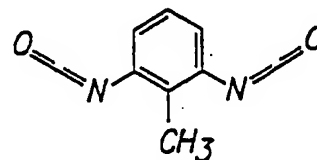
X-219



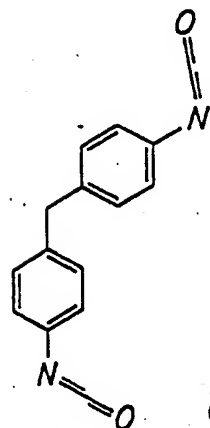
X-222



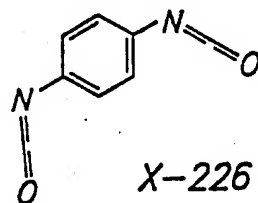
X-223



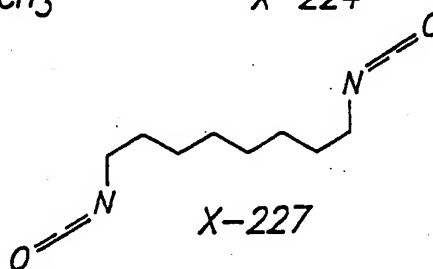
X-224



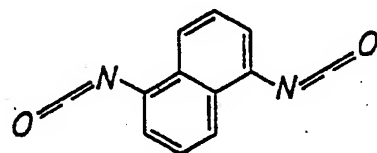
X-225



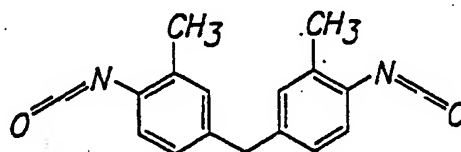
X-226



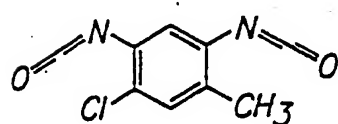
X-227



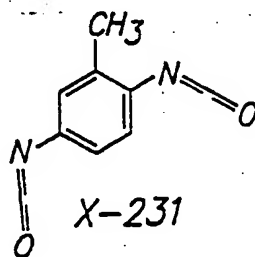
X-228



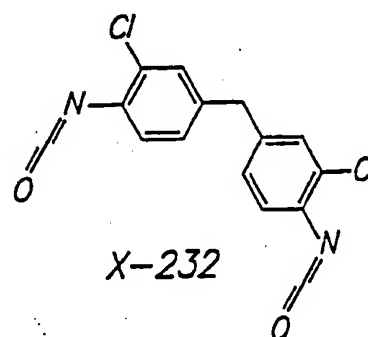
X-229



X-230

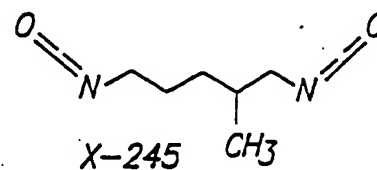
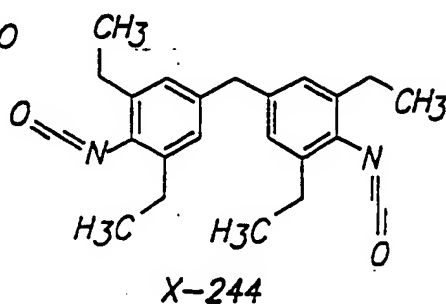
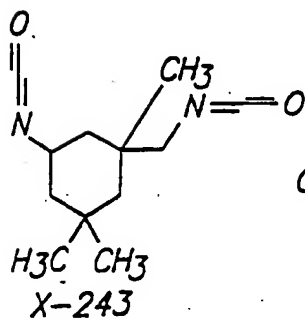
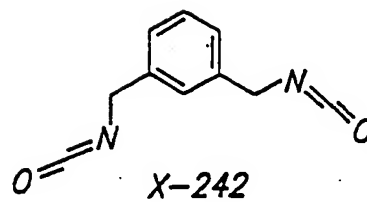
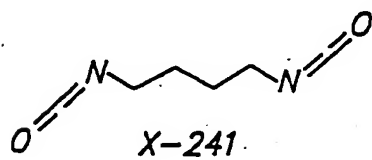
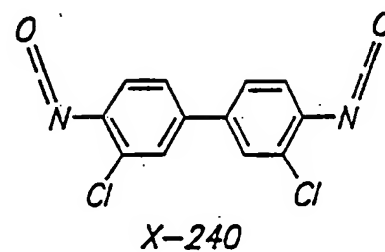
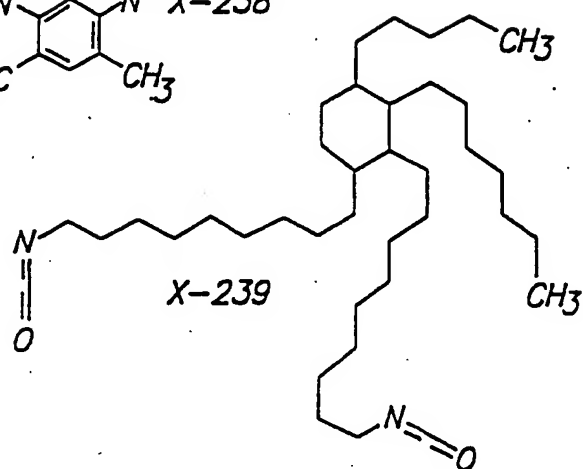
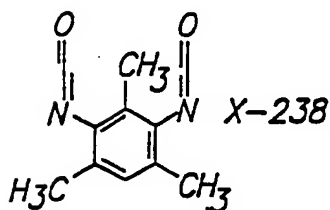
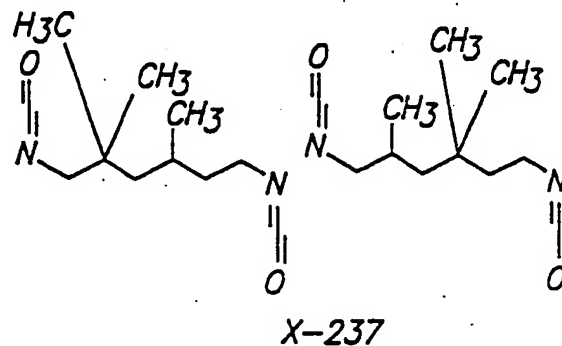
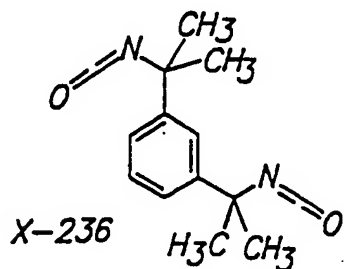
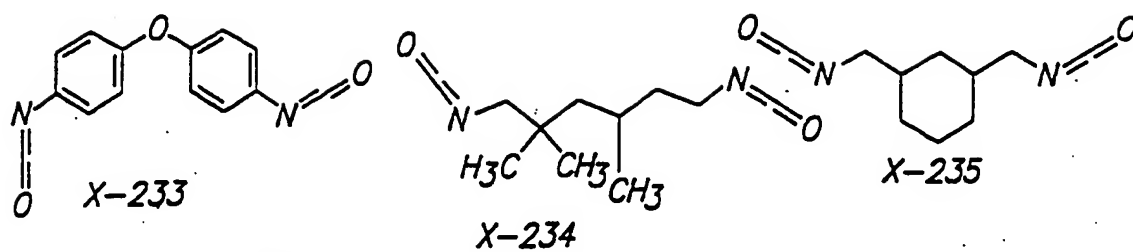


X-231

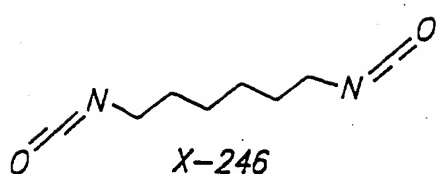


X-232

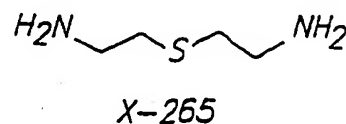
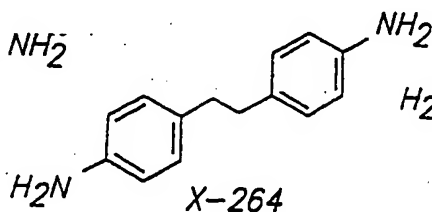
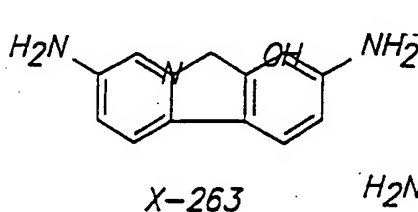
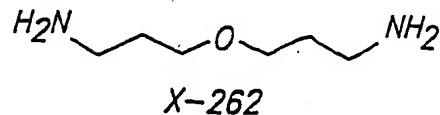
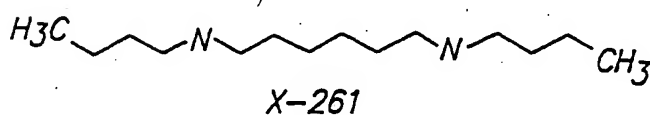
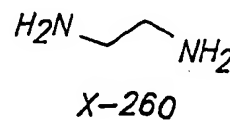
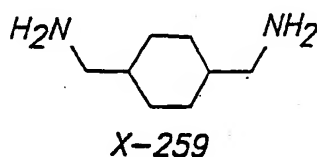
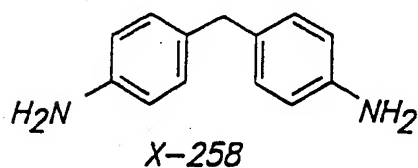
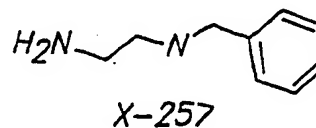
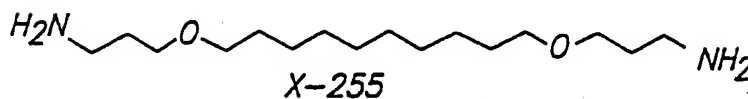
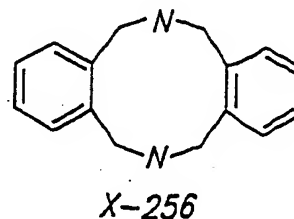
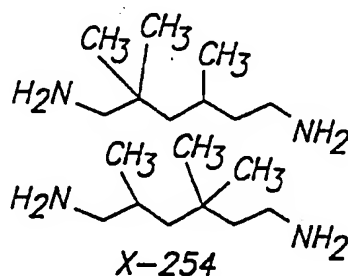
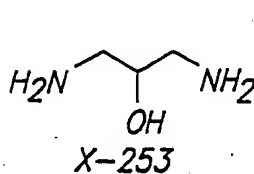
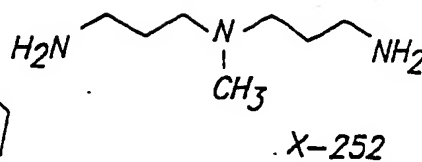
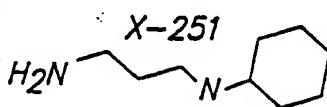
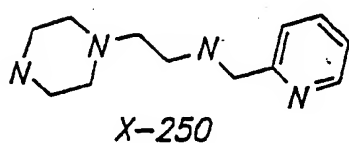
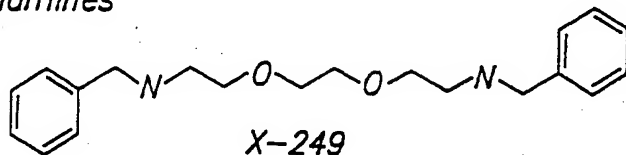
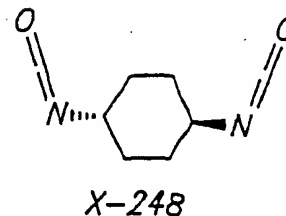
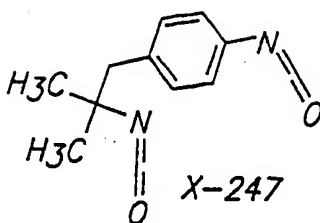
-67 (j)--



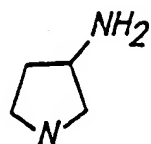
-67 (k)-



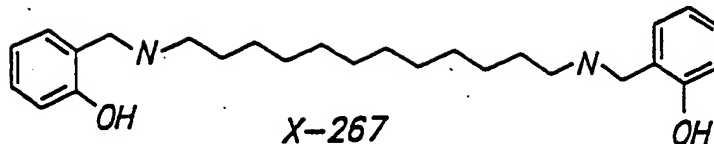
Diamines



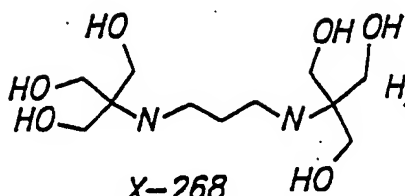
--67 (I)--



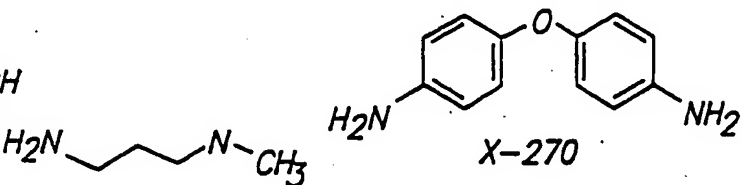
X-266



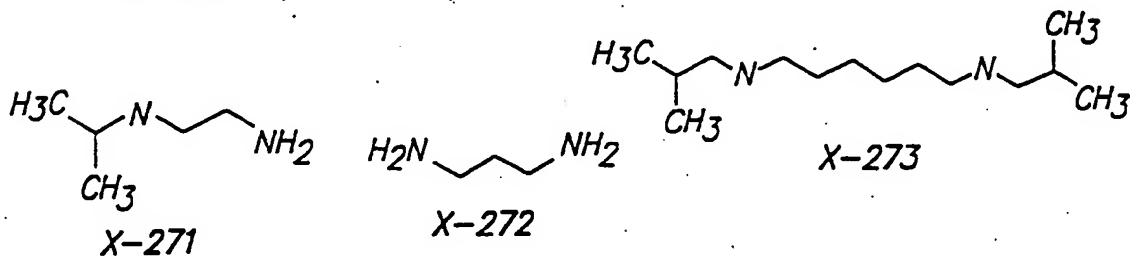
X-267



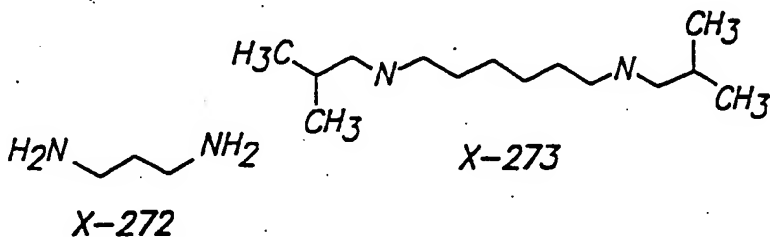
X-268



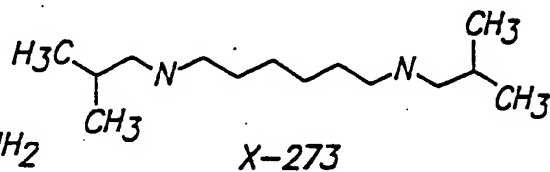
X-269



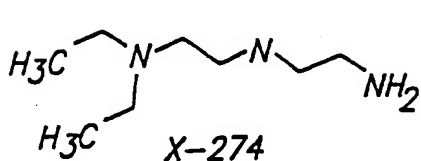
X-271



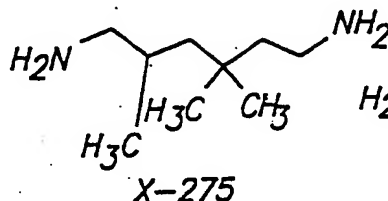
X-272



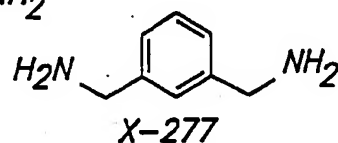
X-273



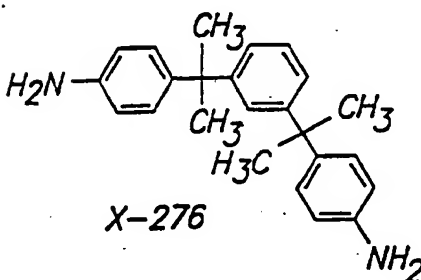
X-274



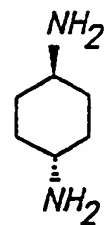
X-275



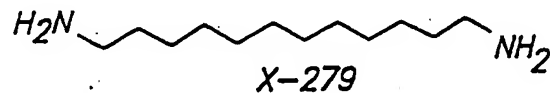
X-277



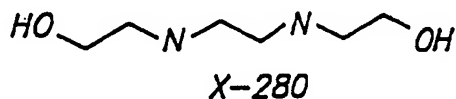
X-276



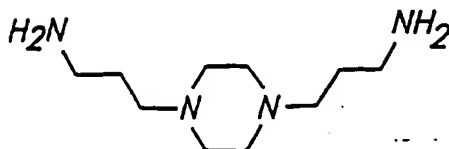
X-278



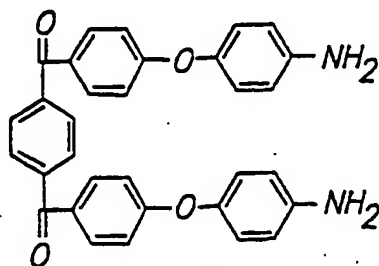
X-279



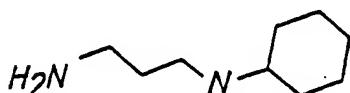
X-280



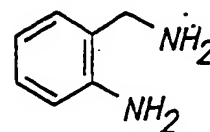
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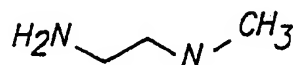
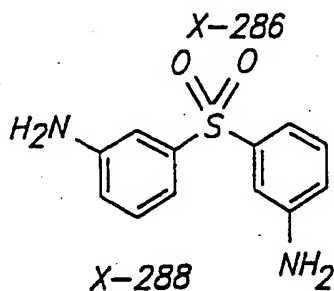
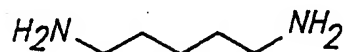
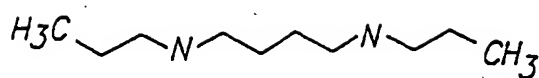
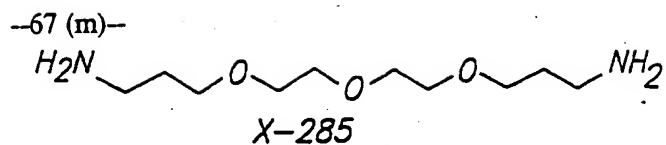


X-282



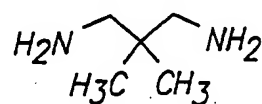
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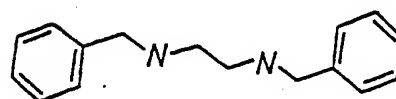


X-289

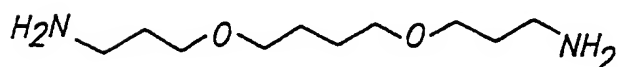
X-287



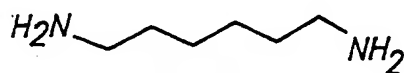
X-290



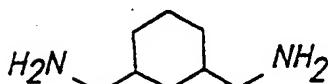
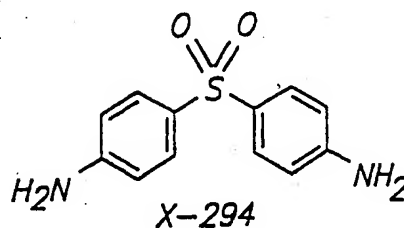
X-292



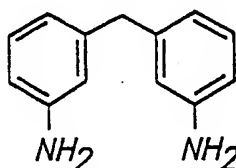
X-291



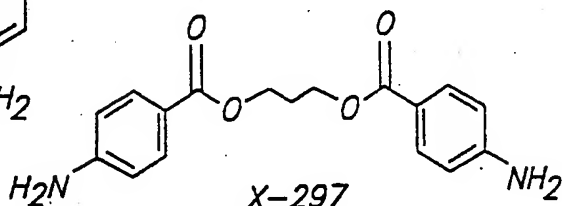
X-293



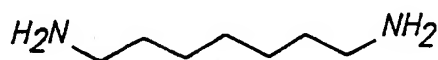
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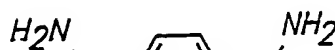
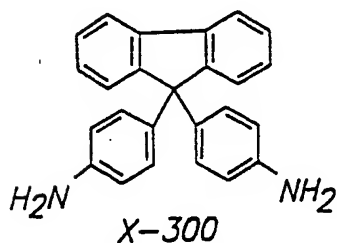
X-296



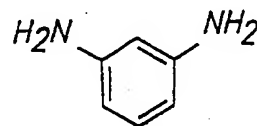
X-298



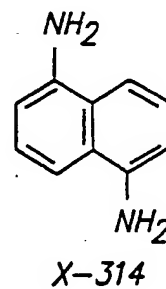
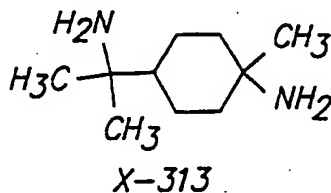
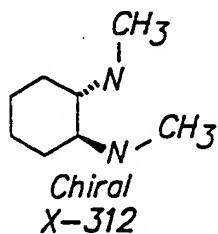
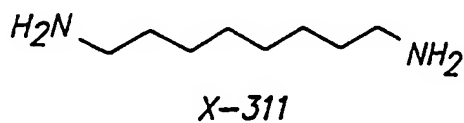
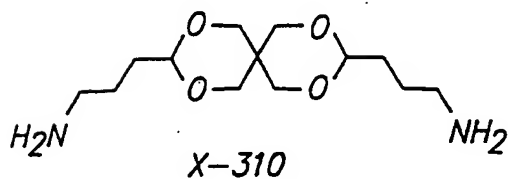
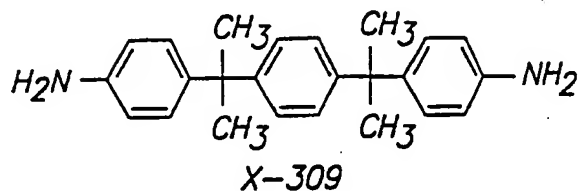
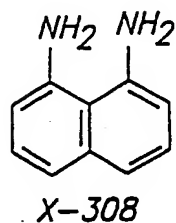
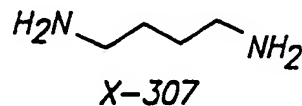
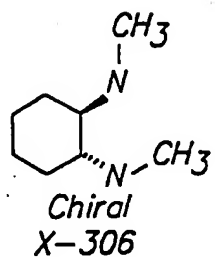
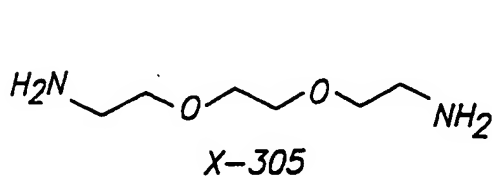
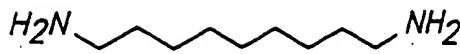
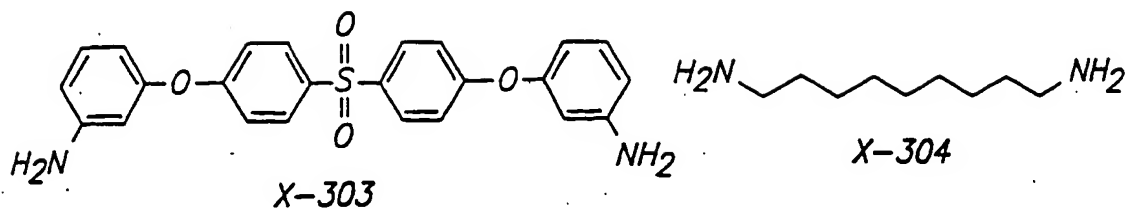
X-299



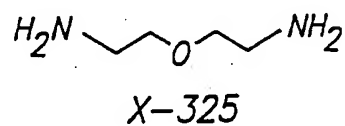
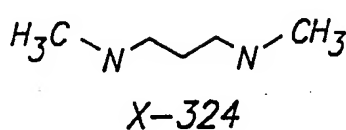
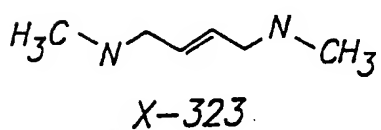
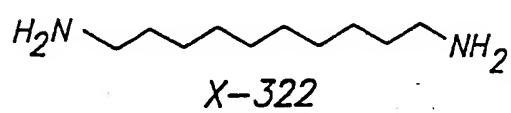
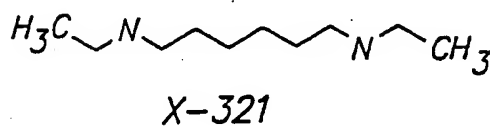
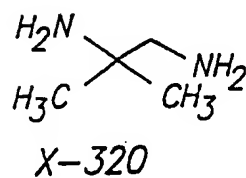
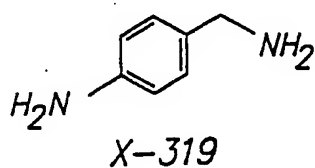
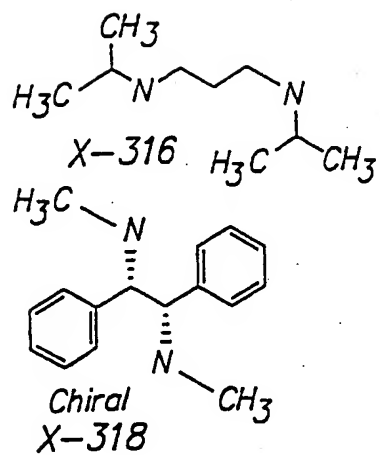
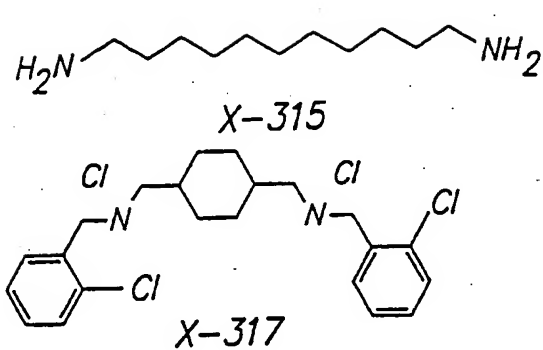
X-301



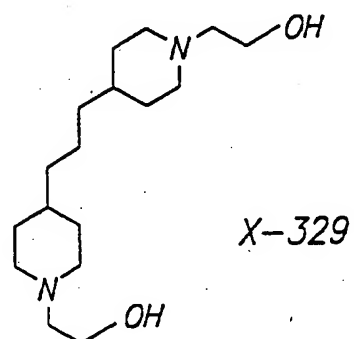
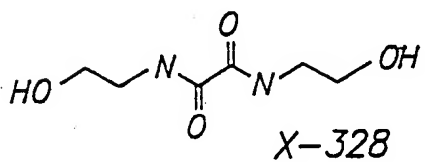
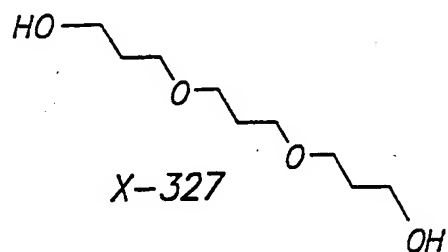
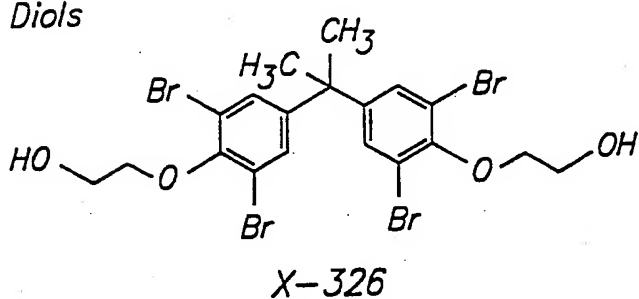
X-302



--67 (o)--

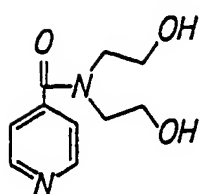


## Diols





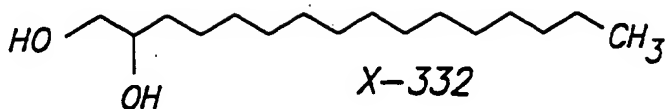
-67 (p)-



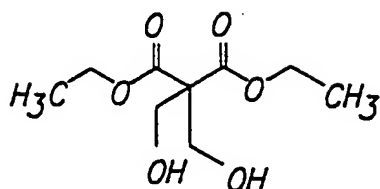
X-330



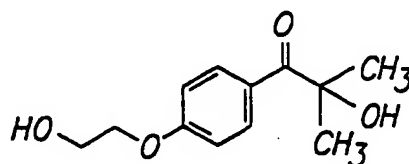
X-331



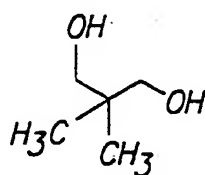
X-332



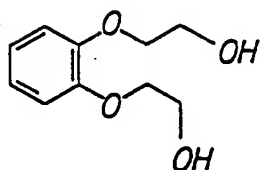
X-333



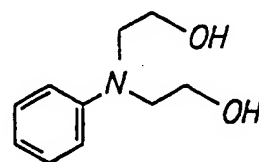
X-334



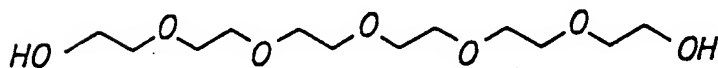
X-335



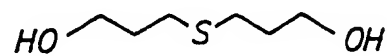
X-336



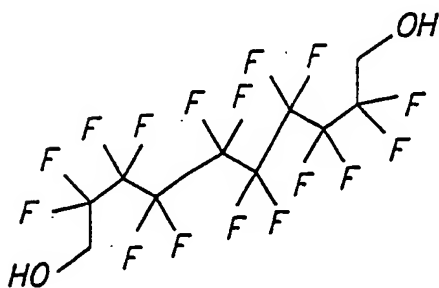
X-337



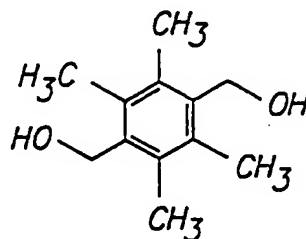
X-338



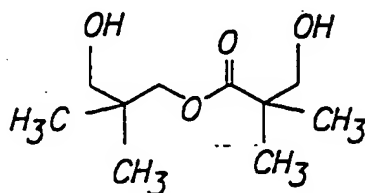
X-339



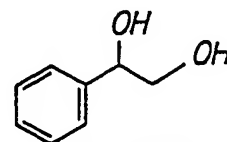
X-340



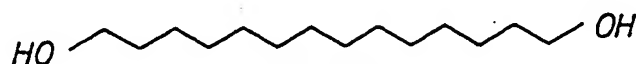
X-341



X-342

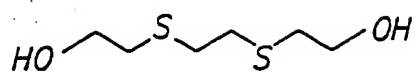


X-343

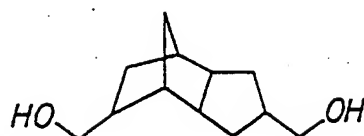


X-344

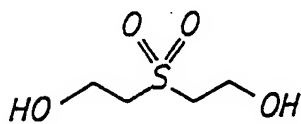
-67 (q)-



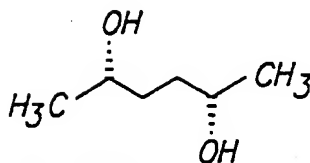
X-345



X-346



X-347



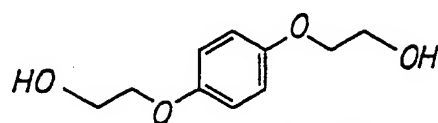
X-348



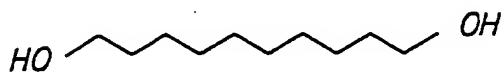
X-349



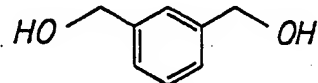
X-350



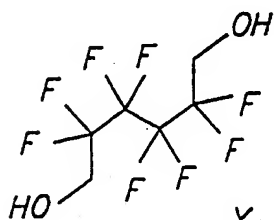
X-351



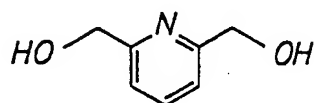
X-352



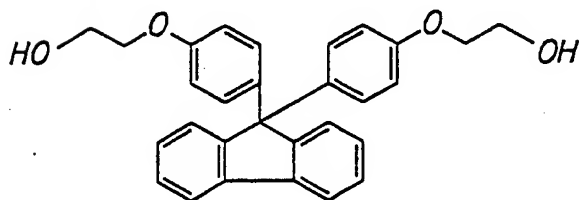
X-353



X-354



X-355



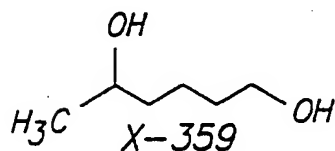
X-356



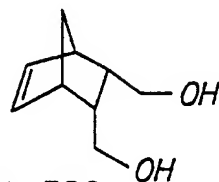
X-357



X-358

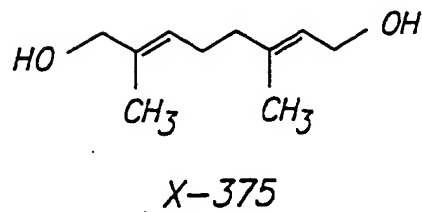
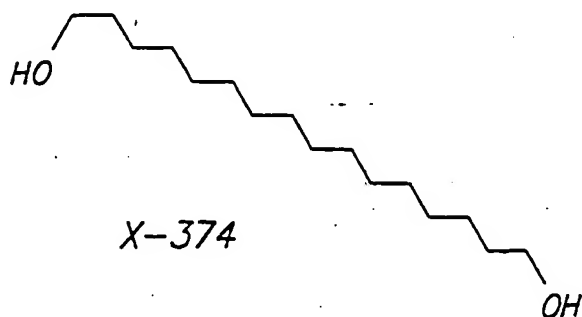
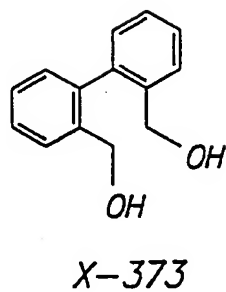
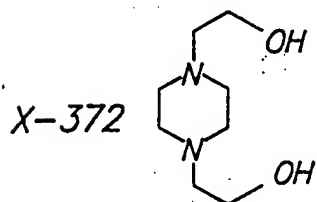
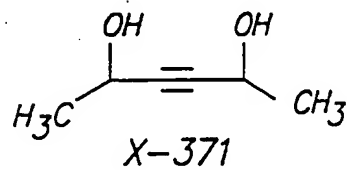
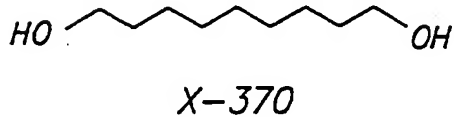
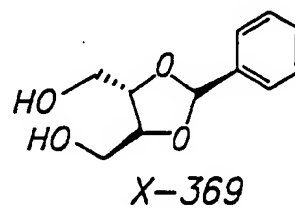
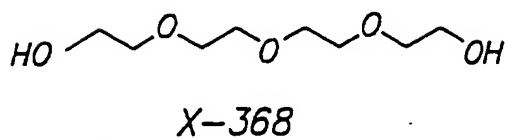
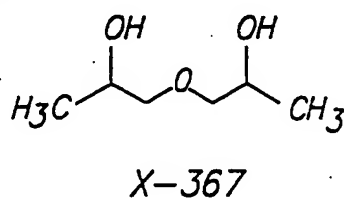
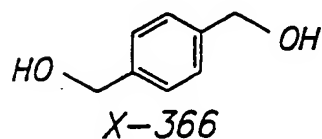
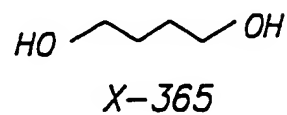
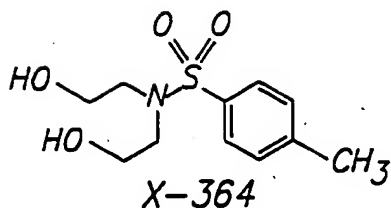
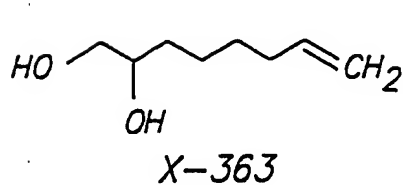
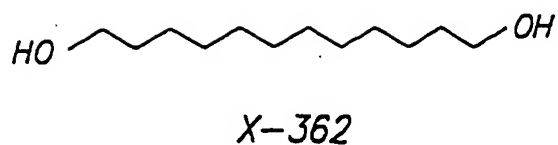
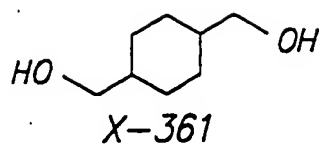


X-359

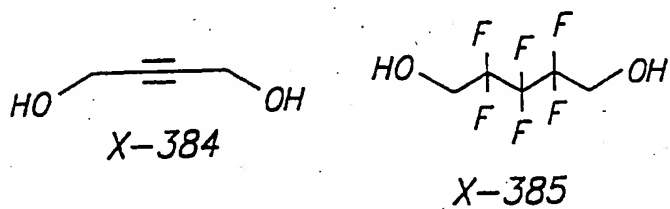
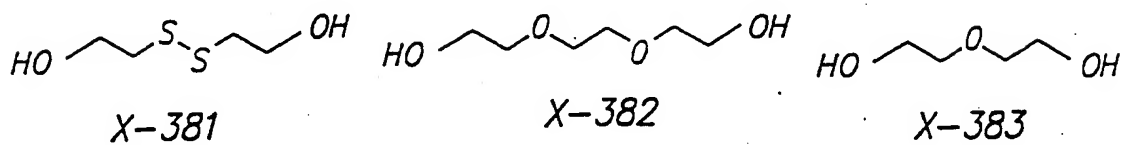
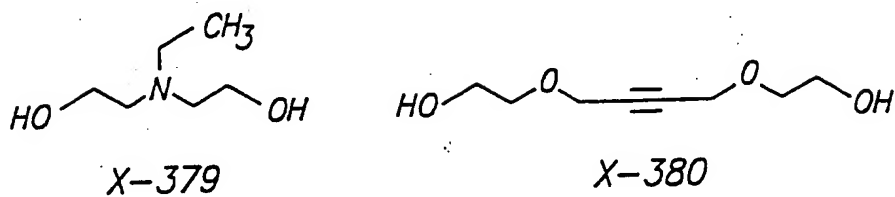
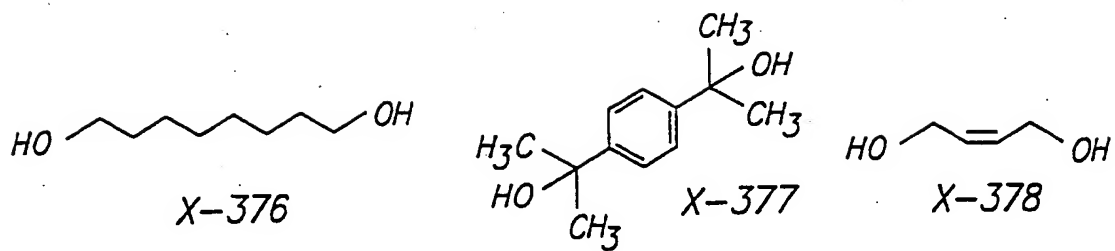


X-360

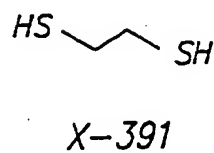
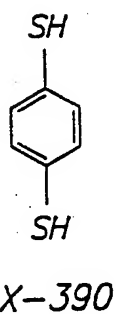
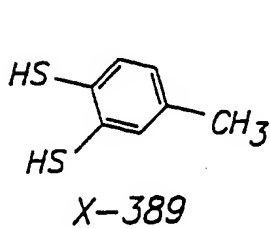
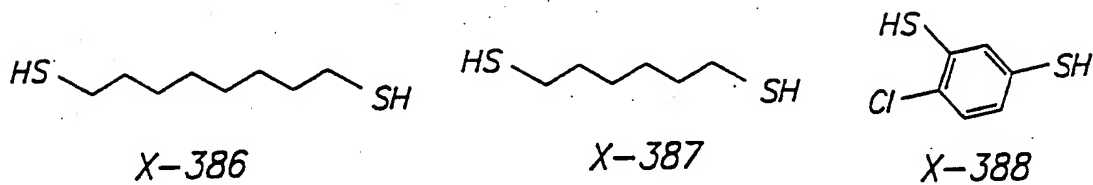
-67 (r)-

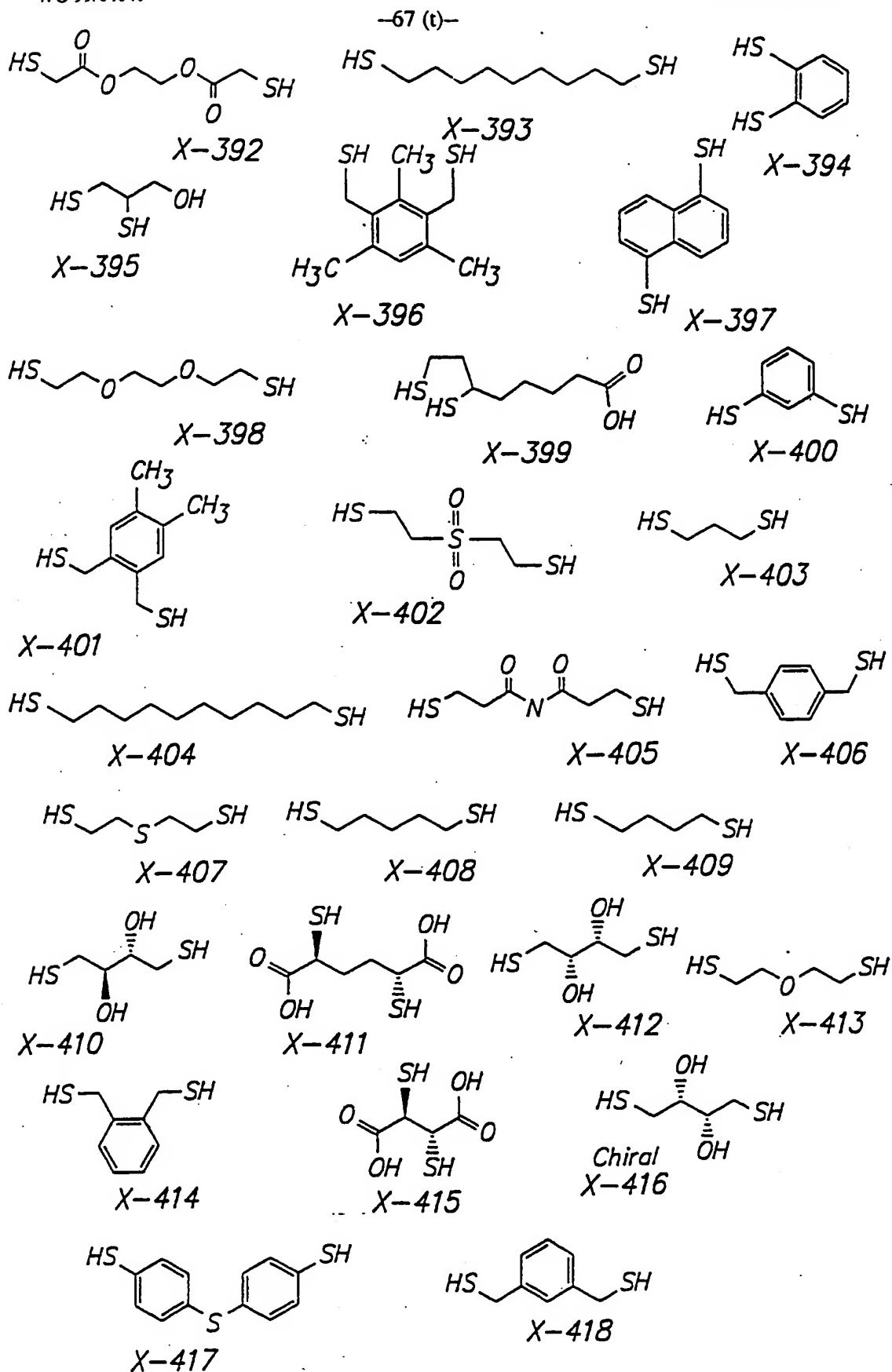


--67 (s)--



## Dithiols





-68-

Representative ligands for use in this invention include, by way of example, L-1 through L-7 as identified above.

Combinations of ligands (L) and linkers (X) per this invention include, by way example only, homo- and hetero-dimers wherein a first ligand is selected from L-1 through L-7 above and the second ligand and linker is selected from the following:

	L-1/X-1-	L-1/X-2-	L-1/X-3-	L-1/X-4-	L-1/X-5-	L-1/X-6-
	L-1/X-7-	L-1/X-8-	L-1/X-9-	L-1/X-10-	L-1/X-11-	L-1/X-12-
	L-1/X-13-	L-1/X-14-	L-1/X-15-	L-1/X-16-	L-1/X-17-	L-1/X-18-
10	L-1/X-19-	L-1/X-20-	L-1/X-21-	L-1/X-22-	L-1/X-23-	L-1/X-24-
	L-1/X-25-	L-1/X-26-	L-1/X-27-	L-1/X-28-	L-1/X-29-	L-1/X-30-
	L-1/X-31-	L-1/X-32-	L-1/X-33-	L-1/X-34-	L-1/X-35-	L-1/X-36-
	L-1/X-37-	L-1/X-38-	L-1/X-39-	L-1/X-40-	L-1/X-41-	L-1/X-42-
	L-1/X-43-	L-1/X-44-	L-1/X-45-	L-1/X-46-	L-1/X-47-	L-1/X-48-
15	L-1/X-49-	L-1/X-50-	L-1/X-51-	L-1/X-52-	L-1/X-53-	L-1/X-54-
	L-1/X-55-	L-1/X-56-	L-1/X-57-	L-1/X-58-	L-1/X-59-	L-1/X-60-
	L-1/X-61-	L-1/X-62-	L-1/X-63-	L-1/X-64-	L-1/X-65-	L-1/X-66-
	L-1/X-67-	L-1/X-68-	L-1/X-69-	L-1/X-70-	L-1/X-71-	L-1/X-72-
	L-1/X-73-	L-1/X-74-	L-1/X-75-	L-1/X-76-	L-1/X-77-	L-1/X-78-
20	L-1/X-79-	L-1/X-80-	L-1/X-81-	L-1/X-82-	L-1/X-83-	L-1/X-84-
	L-1/X-85-	L-1/X-86-	L-1/X-87-	L-1/X-88-	L-1/X-89-	L-1/X-90-
	L-1/X-91-	L-1/X-92-	L-1/X-93-	L-1/X-94-	L-1/X-95-	L-1/X-96-
	L-1/X-97-	L-1/X-98-	L-1/X-99-	L-1/X-100-	L-1/X-101-	L-1/X-102-
	L-1/X-103-	L-1/X-104-	L-1/X-105-	L-1/X-106-	L-1/X-107-	L-1/X-108-
25	L-1/X-109-	L-1/X-110-	L-1/X-111-	L-1/X-112-	L-1/X-113-	L-1/X-114-
	L-1/X-115-	L-1/X-116-	L-1/X-117-	L-1/X-118-	L-1/X-119-	L-1/X-120-
	L-1/X-121-	L-1/X-122-	L-1/X-123-	L-1/X-124-	L-1/X-125-	L-1/X-126-
	L-1/X-127-	L-1/X-128-	L-1/X-129-	L-1/X-130-	L-1/X-131-	L-1/X-132-
	L-1/X-133-	L-1/X-134-	L-1/X-135-	L-1/X-136-	L-1/X-137-	L-1/X-138-
30	L-1/X-139-	L-1/X-140-	L-1/X-141-	L-1/X-142-	L-1/X-143-	L-1/X-144-
	L-1/X-145-	L-1/X-146-	L-1/X-147-	L-1/X-148-	L-1/X-149-	L-1/X-150-
	L-1/X-151-	L-1/X-152-	L-1/X-153-	L-1/X-154-	L-1/X-155-	L-1/X-156-
	L-1/X-157-	L-1/X-158-	L-1/X-159-	L-1/X-160-	L-1/X-161-	L-1/X-162-
	L-1/X-163-	L-1/X-164-	L-1/X-165-	L-1/X-166-	L-1/X-167-	L-1/X-168-
35	L-1/X-169-	L-1/X-170-	L-1/X-171-	L-1/X-172-	L-1/X-177-	L-1/X-178-
	L-1/X-173-	L-1/X-174-	L-1/X-175-	L-1/X-176-	L-1/X-183-	L-1/X-184-
	L-1/X-179-	L-1/X-180-	L-1/X-181-	L-1/X-182-	L-1/X-188-	L-1/X-189-
	L-1/X-185-	L-1/X-186-	L-1/X-187-	L-1/X-188-	L-1/X-189-	L-1/X-190-
	L-1/X-191-	L-1/X-192-	L-1/X-193-	L-1/X-194-	L-1/X-195-	L-1/X-196-
40	L-1/X-197-	L-1/X-198-	L-1/X-199-	L-1/X-200-	L-1/X-201-	L-1/X-202-
	L-1/X-203-	L-1/X-204-	L-1/X-205-	L-1/X-206-	L-1/X-207-	L-1/X-208-
	L-1/X-209-	L-1/X-210-	L-1/X-211-	L-1/X-212-	L-1/X-213-	L-1/X-214-
	L-1/X-215-	L-1/X-216-	L-1/X-217-	L-1/X-218-	L-1/X-219-	L-1/X-220-

	L-1/X-221-	L-1/X-222-	L-1/X-223-	L-1/X-224-	L-1/X-225-	L-1/X-226-
	L-1/X-227-	L-1/X-228-	L-1/X-229-	L-1/X-230-	L-1/X-231-	L-1/X-232-
	L-1/X-233-	L-1/X-234-	L-1/X-235-	L-1/X-236-	L-1/X-237-	L-1/X-238-
	L-1/X-239-	L-1/X-240-	L-1/X-241-	L-1/X-242-	L-1/X-243-	L-1/X-244-
5	L-1/X-245-	L-1/X-246-	L-1/X-247-	L-1/X-248-	L-1/X-249-	L-1/X-250-
	L-1/X-251-	L-1/X-252-	L-1/X-253-	L-1/X-254-	L-1/X-255-	L-1/X-256-
	L-1/X-257-	L-1/X-258-	L-1/X-259-	L-1/X-260-	L-1/X-261-	L-1/X-262-
	L-1/X-263-	L-1/X-264-	L-1/X-265-	L-1/X-266-	L-1/X-267-	L-1/X-268-
	L-1/X-269-	L-1/X-270-	L-1/X-271-	L-1/X-272-	L-1/X-273-	L-1/X-274-
10	L-1/X-275-	L-1/X-276-	L-1/X-277-	L-1/X-278-	L-1/X-279-	L-1/X-280-
	L-1/X-281-	L-1/X-282-	L-1/X-283-	L-1/X-284-	L-1/X-285-	L-1/X-286-
	L-1/X-287-	L-1/X-288-	L-1/X-289-	L-1/X-290-	L-1/X-291-	L-1/X-292-
	L-1/X-293-	L-1/X-294-	L-1/X-295-	L-1/X-296-	L-1/X-297-	L-1/X-298-
	L-1/X-299-	L-1/X-300-	L-1/X-301-	L-1/X-302-	L-1/X-303-	L-1/X-304-
15	L-1/X-305-	L-1/X-306-	L-1/X-307-	L-1/X-308-	L-1/X-309-	L-1/X-310-
	L-1/X-311-	L-1/X-312-	L-1/X-313-	L-1/X-314-	L-1/X-315-	L-1/X-316-
	L-1/X-317-	L-1/X-318-	L-1/X-319-	L-1/X-320-	L-1/X-321-	L-1/X-322-
	L-1/X-323-	L-1/X-324-	L-1/X-325-	L-1/X-326-	L-1/X-327-	L-1/X-328-
	L-1/X-329-	L-1/X-330-	L-1/X-331-	L-1/X-332-	L-1/X-333-	L-1/X-334-
20	L-1/X-335-	L-1/X-336-	L-1/X-337-	L-1/X-338-	L-1/X-339-	L-1/X-340-
	L-1/X-341-	L-1/X-342-	L-1/X-343-	L-1/X-344-	L-1/X-345-	L-1/X-346-
	L-1/X-347-	L-1/X-348-	L-1/X-349-	L-1/X-350-	L-1/X-351-	L-1/X-352-
	L-1/X-353-	L-1/X-354-	L-1/X-355-	L-1/X-356-	L-1/X-357-	L-1/X-358-
	L-1/X-359-	L-1/X-360-	L-1/X-361-	L-1/X-362-	L-1/X-363-	L-1/X-364-
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	L-1/X-377-	L-1/X-378-	L-1/X-379-	L-1/X-380-	L-1/X-381-	L-1/X-382-
	L-1/X-383-	L-1/X-384-	L-1/X-385-	L-1/X-386-	L-1/X-387-	L-1/X-388-
	L-1/X-389-	L-1/X-390-	L-1/X-391-	L-1/X-392-	L-1/X-393-	L-1/X-394-
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	L-1/X-401-	L-1/X-402-	L-1/X-403-	L-1/X-404-	L-1/X-405-	L-1/X-406-
	L-1/X-407-	L-1/X-408-	L-1/X-409-	L-1/X-410-	L-1/X-411-	L-1/X-412-
	L-1/X-413-	L-1/X-414-	L-1/X-415-	L-1/X-416-	L-1/X-417-	L-1/X-418-
	L-2/X-1-	L-2/X-2-	L-2/X-3-	L-2/X-4-	L-2/X-5-	L-2/X-6-
35	L-2/X-7-	L-2/X-8-	L-2/X-9-	L-2/X-10-	L-2/X-11-	L-2/X-12-
	L-2/X-13-	L-2/X-14-	L-2/X-15-	L-2/X-16-	L-2/X-17-	L-2/X-18-
	L-2/X-19-	L-2/X-20-	L-2/X-21-	L-2/X-22-	L-2/X-23-	L-2/X-24-
	L-2/X-25-	L-2/X-26-	L-2/X-27-	L-2/X-28-	L-2/X-29-	L-2/X-30-
	L-2/X-31-	L-2/X-32-	L-2/X-33-	L-2/X-34-	L-2/X-35-	L-2/X-36-
40	L-2/X-37-	L-2/X-38-	L-2/X-39-	L-2/X-40-	L-2/X-41-	L-2/X-42-
	L-2/X-43-	L-2/X-44-	L-2/X-45-	L-2/X-46-	L-2/X-47-	L-2/X-48-
	L-2/X-49-	L-2/X-50-	L-2/X-51-	L-2/X-52-	L-2/X-53-	L-2/X-54-
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	L-2/X-115-	L-2/X-116-	L-2/X-117-	L-2/X-118-	L-2/X-119-	L-2/X-120-
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	L-2/X-139-	L-2/X-140-	L-2/X-141-	L-2/X-142-	L-2/X-143-	L-2/X-144-
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	L-2/X-151-	L-2/X-152-	L-2/X-153-	L-2/X-154-	L-2/X-155-	L-2/X-156-
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	L-2/X-163-	L-2/X-164-	L-2/X-165-	L-2/X-166-	L-2/X-167-	L-2/X-168-
	L-2/X-169-	L-2/X-170-	L-2/X-171-	L-2/X-172-		
	L-2/X-173-	L-2/X-174-	L-2/X-175-	L-2/X-176-	L-2/X-177-	L-2/X-178-
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	L-2/X-197-	L-2/X-198-	L-2/X-199-	L-2/X-200-	L-2/X-201-	L-2/X-202-
	L-2/X-203-	L-2/X-204-	L-2/X-205-	L-2/X-206-	L-2/X-207-	L-2/X-208-
	L-2/X-209-	L-2/X-210-	L-2/X-211-	L-2/X-212-	L-2/X-213-	L-2/X-214-
20	L-2/X-215-	L-2/X-216-	L-2/X-217-	L-2/X-218-	L-2/X-219-	L-2/X-220-
	L-2/X-221-	L-2/X-222-	L-2/X-223-	L-2/X-224-	L-2/X-225-	L-2/X-226-
	L-2/X-227-	L-2/X-228-	L-2/X-229-	L-2/X-230-	L-2/X-231-	L-2/X-232-
	L-2/X-233-	L-2/X-234-	L-2/X-235-	L-2/X-236-	L-2/X-237-	L-2/X-238-
	L-2/X-239-	L-2/X-240-	L-2/X-241-	L-2/X-242-	L-2/X-243-	L-2/X-244-
25	L-2/X-245-	L-2/X-246-	L-2/X-247-	L-2/X-248-	L-2/X-249-	L-2/X-250-
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	L-2/X-287-	L-2/X-288-	L-2/X-289-	L-2/X-290-	L-2/X-291-	L-2/X-292-
	L-2/X-293-	L-2/X-294-	L-2/X-295-	L-2/X-296-	L-2/X-297-	L-2/X-298-
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	L-2/X-305-	L-2/X-306-	L-2/X-307-	L-2/X-308-	L-2/X-309-	L-2/X-310-
	L-2/X-311-	L-2/X-312-	L-2/X-313-	L-2/X-314-	L-2/X-315-	L-2/X-316-
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40	L-2/X-329-	L-2/X-330-	L-2/X-331-	L-2/X-332-	L-2/X-333-	L-2/X-334-
	L-2/X-335-	L-2/X-336-	L-2/X-337-	L-2/X-338-	L-2/X-339-	L-2/X-340-
	L-2/X-341-	L-2/X-342-	L-2/X-343-	L-2/X-344-	L-2/X-345-	L-2/X-346-
	L-2/X-347-	L-2/X-348-	L-2/X-349-	L-2/X-350-	L-2/X-351-	L-2/X-352-
	L-2/X-353-	L-2/X-354-	L-2/X-355-	L-2/X-356-	L-2/X-357-	L-2/X-358-
45	L-2/X-359-	L-2/X-360-	L-2/X-361-	L-2/X-362-	L-2/X-363-	L-2/X-364-
	L-2/X-365-	L-2/X-366-	L-2/X-367-	L-2/X-368-	L-2/X-369-	L-2/X-370-
	L-2/X-371-	L-2/X-372-	L-2/X-373-	L-2/X-374-	L-2/X-375-	L-2/X-376-
	L-2/X-377-	L-2/X-378-	L-2/X-379-	L-2/X-380-	L-2/X-381-	L-2/X-382-
	L-2/X-383-	L-2/X-384-	L-2/X-385-	L-2/X-386-	L-2/X-387-	L-2/X-388-
	L-2/X-389-	L-2/X-390-	L-2/X-391-	L-2/X-392-	L-2/X-393-	L-2/X-394-
50	L-2/X-395-	L-2/X-396-	L-2/X-397-	L-2/X-398-	L-2/X-399-	L-2/X-400-
	L-2/X-401-	L-2/X-402-	L-2/X-403-	L-2/X-404-	L-2/X-405-	L-2/X-406-



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	L-2/X-407- L-2/X-413-	L-2/X-408- L-2/X-414-	L-2/X-409- L-2/X-415-	L-2/X-410- L-2/X-416-	L-2/X-411- L-2/X-417-	L-2/X-412- L-2/X-418-
	L-3/X-1- L-3/X-7-	L-3/X-2- L-3/X-8-	L-3/X-3- L-3/X-9-	L-3/X-4- L-3/X-10-	L-3/X-5- L-3/X-11-	L-3/X-6- L-3/X-12-
5	L-3/X-13- L-3/X-19- L-3/X-25-	L-3/X-14- L-3/X-20- L-3/X-26-	L-3/X-15- L-3/X-21- L-3/X-27-	L-3/X-16- L-3/X-22- L-3/X-28-	L-3/X-17- L-3/X-23- L-3/X-29-	L-3/X-18- L-3/X-24- L-3/X-30-
	L-3/X-31- L-3/X-37-	L-3/X-32- L-3/X-38-	L-3/X-33- L-3/X-39-	L-3/X-34- L-3/X-40-	L-3/X-35- L-3/X-41-	L-3/X-36- L-3/X-42-
10	L-3/X-43- L-3/X-49- L-3/X-55-	L-3/X-44- L-3/X-50- L-3/X-56-	L-3/X-45- L-3/X-51- L-3/X-57-	L-3/X-46- L-3/X-52- L-3/X-58-	L-3/X-47- L-3/X-53- L-3/X-59-	L-3/X-48- L-3/X-54- L-3/X-60-
	L-3/X-61- L-3/X-67-	L-3/X-62- L-3/X-68-	L-3/X-63- L-3/X-69-	L-3/X-64- L-3/X-70-	L-3/X-65- L-3/X-71-	L-3/X-66- L-3/X-72-
15	L-3/X-73- L-3/X-79- L-3/X-85-	L-3/X-74- L-3/X-80- L-3/X-86-	L-3/X-75- L-3/X-81- L-3/X-87-	L-3/X-76- L-3/X-82- L-3/X-88-	L-3/X-77- L-3/X-83- L-3/X-89-	L-3/X-78- L-3/X-84- L-3/X-90-
	L-3/X-91- L-3/X-97-	L-3/X-92- L-3/X-98-	L-3/X-93- L-3/X-99-	L-3/X-94- L-3/X-100-	L-3/X-95- L-3/X-101-	L-3/X-96- L-3/X-102-
20	L-3/X-103- L-3/X-109- L-3/X-115-	L-3/X-104- L-3/X-110- L-3/X-116-	L-3/X-105- L-3/X-111- L-3/X-117-	L-3/X-106- L-3/X-112- L-3/X-118-	L-3/X-107- L-3/X-113- L-3/X-119-	L-3/X-108- L-3/X-114- L-3/X-120-
	L-3/X-121- L-3/X-127-	L-3/X-122- L-3/X-128-	L-3/X-123- L-3/X-129-	L-3/X-124- L-3/X-130-	L-3/X-125- L-3/X-131-	L-3/X-126- L-3/X-132-
25	L-3/X-133- L-3/X-139- L-3/X-145-	L-3/X-134- L-3/X-140- L-3/X-146-	L-3/X-135- L-3/X-141- L-3/X-147-	L-3/X-136- L-3/X-142- L-3/X-148-	L-3/X-137- L-3/X-143- L-3/X-149-	L-3/X-138- L-3/X-144- L-3/X-150-
	L-3/X-151- L-3/X-157-	L-3/X-152- L-3/X-158-	L-3/X-153- L-3/X-159-	L-3/X-154- L-3/X-160-	L-3/X-155- L-3/X-161-	L-3/X-156- L-3/X-162-
30	L-3/X-163- L-3/X-169- L-3/X-173-	L-3/X-164- L-3/X-170- L-3/X-174-	L-3/X-165- L-3/X-171- L-3/X-175-	L-3/X-166- L-3/X-172- L-3/X-176-	L-3/X-167- L-3/X-177- L-3/X-183-	L-3/X-168- L-3/X-178- L-3/X-184-
	L-3/X-179- L-3/X-185-	L-3/X-180- L-3/X-186-	L-3/X-181- L-3/X-187-	L-3/X-182- L-3/X-188-	L-3/X-189- L-3/X-195-	L-3/X-190- L-3/X-196-
35	L-3/X-191- L-3/X-197- L-3/X-203-	L-3/X-192- L-3/X-198- L-3/X-204-	L-3/X-193- L-3/X-199- L-3/X-205-	L-3/X-194- L-3/X-200- L-3/X-206-	L-3/X-201- L-3/X-207- L-3/X-213-	L-3/X-202- L-3/X-208- L-3/X-214-
	L-3/X-209- L-3/X-215-	L-3/X-210- L-3/X-216-	L-3/X-211- L-3/X-217-	L-3/X-212- L-3/X-218-	L-3/X-219- L-3/X-225-	L-3/X-220- L-3/X-226-
40	L-3/X-221- L-3/X-227- L-3/X-233-	L-3/X-222- L-3/X-228- L-3/X-234-	L-3/X-223- L-3/X-229- L-3/X-235-	L-3/X-224- L-3/X-230- L-3/X-236-	L-3/X-231- L-3/X-237- L-3/X-243-	L-3/X-232- L-3/X-238- L-3/X-244-
	L-3/X-239- L-3/X-245-	L-3/X-240- L-3/X-246-	L-3/X-241- L-3/X-247-	L-3/X-242- L-3/X-248-	L-3/X-249- L-3/X-255-	L-3/X-250- L-3/X-256-
45	L-3/X-251- L-3/X-257- L-3/X-263-	L-3/X-252- L-3/X-258- L-3/X-264-	L-3/X-253- L-3/X-259- L-3/X-265-	L-3/X-254- L-3/X-260- L-3/X-266-	L-3/X-255- L-3/X-261- L-3/X-267-	L-3/X-256- L-3/X-262- L-3/X-268-
	L-3/X-269- L-3/X-275-	L-3/X-270- L-3/X-276-	L-3/X-271- L-3/X-277-	L-3/X-272- L-3/X-278-	L-3/X-273- L-3/X-279-	L-3/X-274- L-3/X-280-

	L-3/X-281-	L-3/X-282-	L-3/X-283-	L-3/X-284-	L-3/X-285-	L-3/X-286-
	L-3/X-287-	L-3/X-288-	L-3/X-289-	L-3/X-290-	L-3/X-291-	L-3/X-292-
	L-3/X-293-	L-3/X-294-	L-3/X-295-	L-3/X-296-	L-3/X-297-	L-3/X-298-
	L-3/X-299-	L-3/X-300-	L-3/X-301-	L-3/X-302-	L-3/X-303-	L-3/X-304-
5	L-3/X-305-	L-3/X-306-	L-3/X-307-	L-3/X-308-	L-3/X-309-	L-3/X-310-
	L-3/X-311-	L-3/X-312-	L-3/X-313-	L-3/X-314-	L-3/X-315-	L-3/X-316-
	L-3/X-317-	L-3/X-318-	L-3/X-319-	L-3/X-320-	L-3/X-321-	L-3/X-322-
	L-3/X-323-	L-3/X-324-	L-3/X-325-	L-3/X-326-	L-3/X-327-	L-3/X-328-
	L-3/X-329-	L-3/X-330-	L-3/X-331-	L-3/X-332-	L-3/X-333-	L-3/X-334-
10	L-3/X-335-	L-3/X-336-	L-3/X-337-	L-3/X-338-	L-3/X-339-	L-3/X-340-
	L-3/X-341-	L-3/X-342-	L-3/X-343-	L-3/X-344-	L-3/X-345-	L-3/X-346-
	L-3/X-347-	L-3/X-348-	L-3/X-349-	L-3/X-350-	L-3/X-351-	L-3/X-352-
	L-3/X-353-	L-3/X-354-	L-3/X-355-	L-3/X-356-	L-3/X-357-	L-3/X-358-
	L-3/X-359-	L-3/X-360-	L-3/X-361-	L-3/X-362-	L-3/X-363-	L-3/X-364-
15	L-3/X-365-	L-3/X-366-	L-3/X-367-	L-3/X-368-	L-3/X-369-	L-3/X-370-
	L-3/X-371-	L-3/X-372-	L-3/X-373-	L-3/X-374-	L-3/X-375-	L-3/X-376-
	L-3/X-377-	L-3/X-378-	L-3/X-379-	L-3/X-380-	L-3/X-381-	L-3/X-382-
	L-3/X-383-	L-3/X-384-	L-3/X-385-	L-3/X-386-	L-3/X-387-	L-3/X-388-
	L-3/X-389-	L-3/X-390-	L-3/X-391-	L-3/X-392-	L-3/X-393-	L-3/X-394-
20	L-3/X-395-	L-3/X-396-	L-3/X-397-	L-3/X-398-	L-3/X-399-	L-3/X-400-
	L-3/X-401-	L-3/X-402-	L-3/X-403-	L-3/X-404-	L-3/X-405-	L-3/X-406-
	L-3/X-407-	L-3/X-408-	L-3/X-409-	L-3/X-410-	L-3/X-411-	L-3/X-412-
	L-3/X-413-	L-3/X-414-	L-3/X-415-	L-3/X-416-	L-3/X-417-	L-3/X-418-
	L-4/X-1-	L-4/X-2-	L-4/X-3-	L-4/X-4-	L-4/X-5-	L-4/X-6-
25	L-4/X-7-	L-4/X-8-	L-4/X-9-	L-4/X-10-	L-4/X-11-	L-4/X-12-
	L-4/X-13-	L-4/X-14-	L-4/X-15-	L-4/X-16-	L-4/X-17-	L-4/X-18-
	L-4/X-19-	L-4/X-20-	L-4/X-21-	L-4/X-22-	L-4/X-23-	L-4/X-24-
	L-4/X-25-	L-4/X-26-	L-4/X-27-	L-4/X-28-	L-4/X-29-	L-4/X-30-
	L-4/X-31-	L-4/X-32-	L-4/X-33-	L-4/X-34-	L-4/X-35-	L-4/X-36-
30	L-4/X-37-	L-4/X-38-	L-4/X-39-	L-4/X-40-	L-4/X-41-	L-4/X-42-
	L-4/X-43-	L-4/X-44-	L-4/X-45-	L-4/X-46-	L-4/X-47-	L-4/X-48-
	L-4/X-49-	L-4/X-50-	L-4/X-51-	L-4/X-52-	L-4/X-53-	L-4/X-54-
	L-4/X-55-	L-4/X-56-	L-4/X-57-	L-4/X-58-	L-4/X-59-	L-4/X-60-
	L-4/X-61-	L-4/X-62-	L-4/X-63-	L-4/X-64-	L-4/X-65-	L-4/X-66-
35	L-4/X-67-	L-4/X-68-	L-4/X-69-	L-4/X-70-	L-4/X-71-	L-4/X-72-
	L-4/X-73-	L-4/X-74-	L-4/X-75-	L-4/X-76-	L-4/X-77-	L-4/X-78-
	L-4/X-79-	L-4/X-80-	L-4/X-81-	L-4/X-82-	L-4/X-83-	L-4/X-84-
	L-4/X-85-	L-4/X-86-	L-4/X-87-	L-4/X-88-	L-4/X-89-	L-4/X-90-
	L-4/X-91-	L-4/X-92-	L-4/X-93-	L-4/X-94-	L-4/X-95-	L-4/X-96-
40	L-4/X-97-	L-4/X-98-	L-4/X-99-	L-4/X-100-	L-4/X-101-	L-4/X-102-
	L-4/X-103-	L-4/X-104-	L-4/X-105-	L-4/X-106-	L-4/X-107-	L-4/X-108-
	L-4/X-109-	L-4/X-110-	L-4/X-111-	L-4/X-112-	L-4/X-113-	L-4/X-114-
	L-4/X-115-	L-4/X-116-	L-4/X-117-	L-4/X-118-	L-4/X-119-	L-4/X-120-
	L-4/X-121-	L-4/X-122-	L-4/X-123-	L-4/X-124-	L-4/X-125-	L-4/X-126-
45	L-4/X-127-	L-4/X-128-	L-4/X-129-	L-4/X-130-	L-4/X-131-	L-4/X-132-
	L-4/X-133-	L-4/X-134-	L-4/X-135-	L-4/X-136-	L-4/X-137-	L-4/X-138-
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	L-4/X-145-	L-4/X-146-	L-4/X-147-	L-4/X-148-	L-4/X-149-	L-4/X-150-
	L-4/X-151-	L-4/X-152-	L-4/X-153-	L-4/X-154-	L-4/X-155-	L-4/X-156-
50	L-4/X-157-	L-4/X-158-	L-4/X-159-	L-4/X-160-	L-4/X-161-	L-4/X-162-

	L-4/X-163-	L-4/X-164-	L-4/X-165-	L-4/X-166-	L-4/X-167-	L-4/X-168-
	L-4/X-169-	L-4/X-170-	L-4/X-171-	L-4/X-172-		
	L-4/X-173-	L-4/X-174-	L-4/X-175-	L-4/X-176-	L-4/X-177-	L-4/X-178-
	L-4/X-179-	L-4/X-180-	L-4/X-181-	L-4/X-182-	L-4/X-183-	L-4/X-184-
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	L-4/X-191-	L-4/X-192-	L-4/X-193-	L-4/X-194-	L-4/X-195-	L-4/X-196-
	L-4/X-197-	L-4/X-198-	L-4/X-199-	L-4/X-200-	L-4/X-201-	L-4/X-202-
	L-4/X-203-	L-4/X-204-	L-4/X-205-	L-4/X-206-	L-4/X-207-	L-4/X-208-
	L-4/X-209-	L-4/X-210-	L-4/X-211-	L-4/X-212-	L-4/X-213-	L-4/X-214-
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	L-4/X-221-	L-4/X-222-	L-4/X-223-	L-4/X-224-	L-4/X-225-	L-4/X-226-
	L-4/X-227-	L-4/X-228-	L-4/X-229-	L-4/X-230-	L-4/X-231-	L-4/X-232-
	L-4/X-233-	L-4/X-234-	L-4/X-235-	L-4/X-236-	L-4/X-237-	L-4/X-238-
	L-4/X-239-	L-4/X-240-	L-4/X-241-	L-4/X-242-	L-4/X-243-	L-4/X-244-
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	L-4/X-251-	L-4/X-252-	L-4/X-253-	L-4/X-254-	L-4/X-255-	L-4/X-256-
	L-4/X-257-	L-4/X-258-	L-4/X-259-	L-4/X-260-	L-4/X-261-	L-4/X-262-
	L-4/X-263-	L-4/X-264-	L-4/X-265-	L-4/X-266-	L-4/X-267-	L-4/X-268-
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	L-4/X-317-	L-4/X-318-	L-4/X-319-	L-4/X-320-	L-4/X-321-	L-4/X-322-
	L-4/X-323-	L-4/X-324-	L-4/X-325-	L-4/X-326-	L-4/X-327-	L-4/X-328-
	L-4/X-329-	L-4/X-330-	L-4/X-331-	L-4/X-332-	L-4/X-333-	L-4/X-334-
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	L-4/X-341-	L-4/X-342-	L-4/X-343-	L-4/X-344-	L-4/X-345-	L-4/X-346-
	L-4/X-347-	L-4/X-348-	L-4/X-349-	L-4/X-350-	L-4/X-351-	L-4/X-352-
	L-4/X-353-	L-4/X-354-	L-4/X-355-	L-4/X-356-	L-4/X-357-	L-4/X-358-
	L-4/X-359-	L-4/X-360-	L-4/X-361-	L-4/X-362-	L-4/X-363-	L-4/X-364-
35	L-4/X-365-	L-4/X-366-	L-4/X-367-	L-4/X-368-	L-4/X-369-	L-4/X-370-
	L-4/X-371-	L-4/X-372-	L-4/X-373-	L-4/X-374-	L-4/X-375-	L-4/X-376-
	L-4/X-377-	L-4/X-378-	L-4/X-379-	L-4/X-380-	L-4/X-381-	L-4/X-382-
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	L-4/X-389-	L-4/X-390-	L-4/X-391-	L-4/X-392-	L-4/X-393-	L-4/X-394-
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	L-4/X-401-	L-4/X-402-	L-4/X-403-	L-4/X-404-	L-4/X-405-	L-4/X-406-
	L-4/X-407-	L-4/X-408-	L-4/X-409-	L-4/X-410-	L-4/X-411-	L-4/X-412-
	L-4/X-413-	L-4/X-414-	L-4/X-415-	L-4/X-416-	L-4/X-417-	L-4/X-418-
45	L-5/X-1-	L-5/X-2-	L-5/X-3-	L-5/X-4-	L-5/X-5-	L-5/X-6-
	L-5/X-7-	L-5/X-8-	L-5/X-9-	L-5/X-10-	L-5/X-11-	L-5/X-12-
	L-5/X-13-	L-5/X-14-	L-5/X-15-	L-5/X-16-	L-5/X-17-	L-5/X-18-
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	L-5/X-31-	L-5/X-32-	L-5/X-33-	L-5/X-34-	L-5/X-35-	L-5/X-36-
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-75-

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	L-5/X-353-	L-5/X-354-	L-5/X-355-	L-5/X-356-	L-5/X-357-	L-5/X-358-
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	L-7/X-31-	L-7/X-32-	L-7/X-33-	L-7/X-34-	L-7/X-35-	L-7/X-36-
	L-7/X-37-	L-7/X-38-	L-7/X-39-	L-7/X-40-	L-7/X-41-	L-7/X-42-
	L-7/X-43-	L-7/X-44-	L-7/X-45-	L-7/X-46-	L-7/X-47-	L-7/X-48-
	L-7/X-49-	L-7/X-50-	L-7/X-51-	L-7/X-52-	L-7/X-53-	L-7/X-54-
45	L-7/X-55-	L-7/X-56-	L-7/X-57-	L-7/X-58-	L-7/X-59-	L-7/X-60-
	L-7/X-61-	L-7/X-62-	L-7/X-63-	L-7/X-64-	L-7/X-65-	L-7/X-66-
	L-7/X-67-	L-7/X-68-	L-7/X-69-	L-7/X-70-	L-7/X-71-	L-7/X-72-
	L-7/X-73-	L-7/X-74-	L-7/X-75-	L-7/X-76-	L-7/X-77-	L-7/X-78-
	L-7/X-79-	L-7/X-80-	L-7/X-81-	L-7/X-82-	L-7/X-83-	L-7/X-84-

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	L-7/X-85-	L-7/X-86-	L-7/X-87-	L-7/X-88-	L-7/X-89-	L-7/X-90-
	L-7/X-91-	L-7/X-92-	L-7/X-93-	L-7/X-94-	L-7/X-95-	L-7/X-96-
	L-7/X-97-	L-7/X-98-	L-7/X-99-	L-7/X-100-	L-7/X-101-	L-7/X-102-
	L-7/X-103-	L-7/X-104-	L-7/X-105-	L-7/X-106-	L-7/X-107-	L-7/X-108-
5	L-7/X-109-	L-7/X-110-	L-7/X-111-	L-7/X-112-	L-7/X-113-	L-7/X-114-
	L-7/X-115-	L-7/X-116-	L-7/X-117-	L-7/X-118-	L-7/X-119-	L-7/X-120-
	L-7/X-121-	L-7/X-122-	L-7/X-123-	L-7/X-124-	L-7/X-125-	L-7/X-126-
	L-7/X-127-	L-7/X-128-	L-7/X-129-	L-7/X-130-	L-7/X-131-	L-7/X-132-
	L-7/X-133-	L-7/X-134-	L-7/X-135-	L-7/X-136-	L-7/X-137-	L-7/X-138-
10	L-7/X-139-	L-7/X-140-	L-7/X-141-	L-7/X-142-	L-7/X-143-	L-7/X-144-
	L-7/X-145-	L-7/X-146-	L-7/X-147-	L-7/X-148-	L-7/X-149-	L-7/X-150-
	L-7/X-151-	L-7/X-152-	L-7/X-153-	L-7/X-154-	L-7/X-155-	L-7/X-156-
	L-7/X-157-	L-7/X-158-	L-7/X-159-	L-7/X-160-	L-7/X-161-	L-7/X-162-
	L-7/X-163-	L-7/X-164-	L-7/X-165-	L-7/X-166-	L-7/X-167-	L-7/X-168-
15	L-7/X-169-	L-7/X-170-	L-7/X-171-	L-7/X-172-		
	L-7/X-173-	L-7/X-174-	L-7/X-175-	L-7/X-176-	L-7/X-177-	L-7/X-178-
	L-7/X-179-	L-7/X-180-	L-7/X-181-	L-7/X-182-	L-7/X-183-	L-7/X-184-
	L-7/X-185-	L-7/X-186-	L-7/X-187-	L-7/X-188-	L-7/X-189-	L-7/X-190-
	L-7/X-191-	L-7/X-192-	L-7/X-193-	L-7/X-194-	L-7/X-195-	L-7/X-196-
20	L-7/X-197-	L-7/X-198-	L-7/X-199-	L-7/X-200-	L-7/X-201-	L-7/X-202-
	L-7/X-203-	L-7/X-204-	L-7/X-205-	L-7/X-206-	L-7/X-207-	L-7/X-208-
	L-7/X-209-	L-7/X-210-	L-7/X-211-	L-7/X-212-	L-7/X-213-	L-7/X-214-
	L-7/X-215-	L-7/X-216-	L-7/X-217-	L-7/X-218-	L-7/X-219-	L-7/X-220-
	L-7/X-221-	L-7/X-222-	L-7/X-223-	L-7/X-224-	L-7/X-225-	L-7/X-226-
25	L-7/X-227-	L-7/X-228-	L-7/X-229-	L-7/X-230-	L-7/X-231-	L-7/X-232-
	L-7/X-233-	L-7/X-234-	L-7/X-235-	L-7/X-236-	L-7/X-237-	L-7/X-238-
	L-7/X-239-	L-7/X-240-	L-7/X-241-	L-7/X-242-	L-7/X-243-	L-7/X-244-
	L-7/X-245-	L-7/X-246-	L-7/X-247-	L-7/X-248-	L-7/X-249-	L-7/X-250-
	L-7/X-251-	L-7/X-252-	L-7/X-253-	L-7/X-254-	L-7/X-255-	L-7/X-256-
30	L-7/X-257-	L-7/X-258-	L-7/X-259-	L-7/X-260-	L-7/X-261-	L-7/X-262-
	L-7/X-263-	L-7/X-264-	L-7/X-265-	L-7/X-266-	L-7/X-267-	L-7/X-268-
	L-7/X-269-	L-7/X-270-	L-7/X-271-	L-7/X-272-	L-7/X-273-	L-7/X-274-
	L-7/X-275-	L-7/X-276-	L-7/X-277-	L-7/X-278-	L-7/X-279-	L-7/X-280-
	L-7/X-281-	L-7/X-282-	L-7/X-283-	L-7/X-284-	L-7/X-285-	L-7/X-286-
35	L-7/X-287-	L-7/X-288-	L-7/X-289-	L-7/X-290-	L-7/X-291-	L-7/X-292-
	L-7/X-293-	L-7/X-294-	L-7/X-295-	L-7/X-296-	L-7/X-297-	L-7/X-298-
	L-7/X-299-	L-7/X-300-	L-7/X-301-	L-7/X-302-	L-7/X-303-	L-7/X-304-
	L-7/X-305-	L-7/X-306-	L-7/X-307-	L-7/X-308-	L-7/X-309-	L-7/X-310-
	L-7/X-311-	L-7/X-312-	L-7/X-313-	L-7/X-314-	L-7/X-315-	L-7/X-316-
40	L-7/X-317-	L-7/X-318-	L-7/X-319-	L-7/X-320-	L-7/X-321-	L-7/X-322-
	L-7/X-323-	L-7/X-324-	L-7/X-325-	L-7/X-326-	L-7/X-327-	L-7/X-328-
	L-7/X-329-	L-7/X-330-	L-7/X-331-	L-7/X-332-	L-7/X-333-	L-7/X-334-
	L-7/X-335-	L-7/X-336-	L-7/X-337-	L-7/X-338-	L-7/X-339-	L-7/X-340-
	L-7/X-341-	L-7/X-342-	L-7/X-343-	L-7/X-344-	L-7/X-345-	L-7/X-346-
45	L-7/X-347-	L-7/X-348-	L-7/X-349-	L-7/X-350-	L-7/X-351-	L-7/X-352-
	L-7/X-353-	L-7/X-354-	L-7/X-355-	L-7/X-356-	L-7/X-357-	L-7/X-358-
	L-7/X-359-	L-7/X-360-	L-7/X-361-	L-7/X-362-	L-7/X-363-	L-7/X-364-
	L-7/X-365-	L-7/X-366-	L-7/X-367-	L-7/X-368-	L-7/X-369-	L-7/X-370-
	L-7/X-371-	L-7/X-372-	L-7/X-373-	L-7/X-374-	L-7/X-375-	L-7/X-376-
50	L-7/X-377-	L-7/X-378-	L-7/X-379-	L-7/X-380-	L-7/X-381-	L-7/X-382-
	L-7/X-383-	L-7/X-384-	L-7/X-385-	L-7/X-386-	L-7/X-387-	L-7/X-388-

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	L-7/X-389-	L-7/X-390-	L-7/X-391-	L-7/X-392-	L-7/X-393-	L-7/X-394-
	L-7/X-395-	L-7/X-396-	L-7/X-397-	L-7/X-398-	L-7/X-399-	L-7/X-400-
	L-7/X-401-	L-7/X-402-	L-7/X-403-	L-7/X-404-	L-7/X-405-	L-7/X-406-
	L-7/X-407-	L-7/X-408-	L-7/X-409-	L-7/X-410-	L-7/X-411-	L-7/X-412-
5	L-7/X-413-	L-7/X-414-	L-7/X-415-	L-7/X-416-	L-7/X-417-	L-7/X-418-

### Pharmaceutical Formulations

When employed as pharmaceuticals, the compounds of the invention are usually administered in the form of pharmaceutical compositions. These compounds can be administered by a variety of routes including oral, rectal, 10 transdermal, subcutaneous, intravenous, intramuscular, and intranasal. These compounds are effective as both injectable and oral compositions. Such compositions are prepared in a manner well known in the pharmaceutical art and comprise at least one active compound.

This invention also includes pharmaceutical compositions which contain, as 15 the active ingredient, one or more of the compounds of the invention associated with pharmaceutically acceptable carriers. In making the compositions of this invention, the active ingredient is usually mixed with an excipient, diluted by an excipient or enclosed within such a carrier which can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be 20 a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and 25 hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

In preparing a formulation, it may be necessary to mill the active



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compound to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it ordinarily is milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size is normally adjusted by milling to provide a substantially uniform distribution in the formulation, e.g. about 40 mesh.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, sterile water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 5 to about 100 mg, more usually about 10 to about 30 mg, of the active ingredient. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. Preferably, the compound of the invention is employed at no more than about 20 weight percent of the pharmaceutical composition, more preferably no more than about 15 weight percent, with the balance being pharmaceutically inert carrier(s).

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The active compound is effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. It will be understood, however, that the amount of the compound actually administered will be determined by a physician or veterinarian, in the light of the relevant  
5 circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered and its relative activity, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

For preparing solid compositions such as tablets, the principal active  
10 ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally  
15 effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then subdivided into unit dosage forms of the type described above containing from, for example, 0.1 to about 500 mg of the active ingredient of the present invention.

The tablets or pills of the present invention may be coated or otherwise  
20 compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into the  
25 duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids

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and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous  
5 solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as corn oil, cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or  
10 mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described *supra*. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be inhaled  
15 directly from the nebulizing device or the nebulizing device may be attached to a face mask tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

The following formulation examples illustrate representative  
20 pharmaceutical compositions of the present invention.

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Formulation Example 1

Hard gelatin capsules containing the following ingredients are prepared:

	<u>Ingredient</u>	<u>Quantity</u> <u>(mg/capsule)</u>
5	Active Ingredient	30.0
	Starch	305.0
	Magnesium stearate	5.0

The above ingredients are mixed and filled into hard gelatin capsules in 340 mg quantities.

10

Formulation Example 2

A tablet formula is prepared using the ingredients below:

	<u>Ingredient</u>	<u>Quantity</u> <u>(mg/tablet)</u>
	Active Ingredient	25.0
15	Cellulose, microcrystalline	200.0
	Colloidal silicon dioxide	10.0
	Stearic acid	5.0

The components are blended and compressed to form tablets. each weighing 240 mg.

20

Formulation Example 3

A dry powder inhaler formulation is prepared containing the following components:

	<u>Ingredient</u>	<u>Weight %</u>
	Active Ingredient	5
25	Lactose	95

The active ingredient is mixed with the lactose and the mixture is added to a dry powder inhaling appliance.

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Formulation Example 4

Tablets, each containing 30 mg of active ingredient, are prepared as follows:

	<u>Ingredient</u>	<u>Quantity</u> <u>(mg/tablet)</u>
5	Active Ingredient	30.0 mg
	Starch	45.0 mg
	Microcrystalline cellulose	35.0 mg
	Polyvinylpyrrolidone	
	(as 10% solution in sterile water)	4.0 mg
10	Sodium carboxymethyl starch	4.5 mg
	Magnesium stearate	0.5 mg
	Talc	<u>1.0 mg</u>
	Total	120 mg

- 15 The active ingredient, starch and cellulose are passed through a No. 20 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders, which are then passed through a 16 mesh U.S. sieve. The granules so produced are dried at 50° to 60°C and passed through a 16 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and
- 20 talc, previously passed through a No. 30 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 120 mg.

Formulation Example 5

Capsules, each containing 40 mg of medicament are made as follows:

	<u>Ingredient</u>	<u>Quantity</u> <u>(mg/capsule)</u>
25	Active Ingredient	40.0 mg
	Starch	109.0 mg
	Magnesium stearate	<u>1.0 mg</u>
30	Total	150.0 mg

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The active ingredient, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 150 mg quantities.

Formulation Example 6

- 5           Suppositories, each containing 25 mg of active ingredient are made as follows:

<u>Ingredient</u>	<u>Amount</u>
Active Ingredient	25 mg
Saturated fatty acid glycerides to	2,000 mg

- 10           The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2.0 g capacity and allowed to cool.

Formulation Example 7

- 15           Suspensions, each containing 50 mg of medicament per 5.0 mL dose are made as follows:

	<u>Ingredient</u>	<u>Amount</u>
	Active Ingredient	50.0 mg
	Xanthan gum	4.0 mg
20	Sodium carboxymethyl cellulose (11%)	
	Microcrystalline cellulose (89%)	50.0 mg
	Sucrose	1.75 g
	Sodium benzoate	10.0 mg
	Flavor and Color	q.v.
25	Purified water to	5.0 mL

The active ingredient, sucrose and xanthan gum are blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously made solution of the microcrystalline cellulose and sodium carboxymethyl cellulose in water. The sodium benzoate, flavor, and color are diluted with some of the water

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and added with stirring. Sufficient water is then added to produce the required volume.

#### Formulation Example 8

5	<u>Ingredient</u>	<u>Quantity</u> <u>(mg/capsule)</u>
	Active Ingredient	15.0 mg
	Starch	407.0 mg
	Magnesium stearate	<u>3.0 mg</u>
	Total	425.0 mg

- 10 The active ingredient, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 425.0 mg quantities.

#### Formulation Example 9

A formulation may be prepared as follows:

15	<u>Ingredient</u>	<u>Quantity</u>
	Active Ingredient	5.0 mg
	Corn Oil	1.0 mL

#### Formulation Example 10

A topical formulation may be prepared as follows:

20	<u>Ingredient</u>	<u>Quantity</u>
	Active Ingredient	1-10 g
	Emulsifying Wax	30 g
	Liquid Paraffin	20 g
	White Soft Paraffin	to 100 g

- 25 The white soft paraffin is heated until molten. The liquid paraffin and emulsifying wax are incorporated and stirred until dissolved. The active

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ingredient is added and stirring is continued until dispersed. The mixture is then cooled until solid.

Another preferred formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. See, e.g., U.S. Patent 5,023,252, issued June 11, 1991, herein incorporated by reference. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

Frequently, it will be desirable or necessary to introduce the pharmaceutical composition to the brain, either directly or indirectly. Direct techniques usually involve placement of a drug delivery catheter into the host's ventricular system to bypass the blood-brain barrier. One such implantable delivery system used for the transport of biological factors to specific anatomical regions of the body is described in U.S. Patent 5,011,472, which is herein incorporated by reference.

Indirect techniques, which are generally preferred, usually involve formulating the compositions to provide for drug latentiation by the conversion of hydrophilic drugs into lipid-soluble drugs. Latentiation is generally achieved through blocking of the hydroxy, carbonyl, sulfate, and primary amine groups present on the drug to render the drug more lipid soluble and amenable to transportation across the blood-brain barrier. Alternatively, the delivery of hydrophilic drugs may be enhanced by intra-arterial infusion of hypertonic solutions which can transiently open the blood-brain barrier.



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Other suitable formulations for use in the present invention can be found in *Remington's Pharmaceutical Sciences*, Mace Publishing Company, Philadelphia, PA, 17<sup>th</sup> Ed (1985).

5       The effectiveness of the compounds made according to the invention described herein can be tested for efficacy and affinity by various techniques known in the art. For example, competitive assays with radiolabeled glycine or glutamate may be used to test the efficacy of a multi-binding ligand compound as described herein which includes one or more ligand which is a glutamate or glycine partial agonist or antagonist.

10       Further, the affinity and efficacy of a multi-binding ligand compound as described herein for various potential binding sites on the NMDA receptor can be tested by patch clamp techniques as known in the art. Using such techniques, the affinity of the agonist, partial agonist or antagonist compounds can be measured, as well as the binding kinetics of the compound. Similarly, high throughput  
15       radioligand binding assays can be used to determine the activity of antagonists at any receptor site, and to distinguish between antagonist, partial agonist and agonist activity.

Specifically, the efficacy of the compounds of the invention may be evaluated in a variety of *in vitro* assays as known to those skilled in the art. For  
20       example, the selectivity of compounds for NMDA receptors may be determined according to the method of Kleckner, NW, et al. (1999) 289(2):886. The ability of compounds to inhibit NMDA receptor mediated production of cGMP may be assessed in cultures of cerebral neurons as set forth in Gonzales, JM., et al. *Anesthesiology*, 82(1):205.

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The effectiveness or activity of the compounds can also be tested *in vivo* using several methods well known to those skilled in the art. The analgesic effect of the compounds may be determined in patients with chronic pain according to the methods of Rabben, T., et al. *J. Pharmacol Exp Ther.* (1999) 289(2):1060. The  
5 anticonvulsant efficacy of NMDA receptor antagonists may be determined in experimentally induced convulsions and seizures following the methods set forth by Witkin, JM et al. *J. Pharmacol. Exp. Ther.* (1999) 289(2):703 and McDonough, J, et al. *Pharmacol., Biochem. Behav.* (1995) 51(2/3):249. The efficacy of the compounds of the invention on hypoxia may also be evaluated using  
10 the method of Schulz et al. as set forth in *Cell Death Differ.* (1998) 10(2):221. The protective effect of compounds on optic nerve degeneration as well as other peripheral neuropathy may be assessed according to the method of Schwartz, M., et al. as set forth in *Euro J. Ophthalmol.* (1999) 9, supplement 1:S9. *In vivo* potency of compounds on motor neuron dysfunction may be tested in mnd mice  
15 (Mennini, T, et al. *Eur. J. Neurosci.* (1999) 11(5):1647). The effect of compounds of the invention on a rat model of Parkinsons disease may be evaluated following the method of Piallat, B., et al. (*J Neural Transm* suppl. (1999) 55:71, while the ability of the compounds of the invention to act as behavior modifiers and to enhance memory may be determined in mice (Suzuki, T, et al. *Life Sci.*  
20 64(12):PL151) and rats (Mason, KI., et al. *Brain Res Bull.* 48(1):65).

Other techniques for measuring the efficacy and binding kinetics or affinity of the herein described multi-binding ligand compounds are known to those in the art.

#### Utility

25 The multibinding agents of the present invention are useful for modulating the NMDA receptor. The modulation of the receptor affects cation transport, particularly calcium and sodium transport. Further, modulation of these receptor

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sites leads to modulation of the effects of excitatory amino acids. These effects are useful in treating mammalian conditions modulated by the NMDA receptor such as pain, but also including, for example, Alzheimer's, cognitive disorder, dementia, schizophrenia, ocular disease, AIDS-related complex, peripheral neuropathy, CV ischemia, infarction, stroke, motor neuron disease, epilepsy, seizure, convulsions, neurodegenerative disease, micturition disorders, migraine, Parkinson's disease, psychosis, Huntingdon's chorea and cardiac failure.

In order to further illustrate the present invention and advantages thereof, the following specific examples are given but are not meant to limit the scope of the claims in any way.

### EXAMPLES

In the Preparations and Examples below, all temperatures are in degrees Celsius (unless otherwise indicated) and all percentages are weight percentages (also unless otherwise indicated).

Preparations 1-57 and Examples 1-23 are given as representative examples of methods for preparing compounds of this invention.

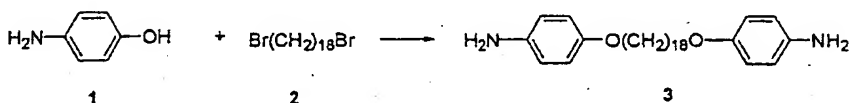
In the Procedures and Examples below, the following abbreviations have the following meanings. If an abbreviation is not defined, it has its generally accepted meaning.

20	Å	= Angstroms
	cm	= centimeter
	DIC	= 2-dimethylaminoisopropyl chloride hydrochloride
	DCC	= <i>N,N</i> -dicyclohexylcarbodiimide
	DCM	= dichloromethane
25	DIPEA	= diisopropylethylamine
	DMA	= <i>N,N</i> -dimethylacetamide

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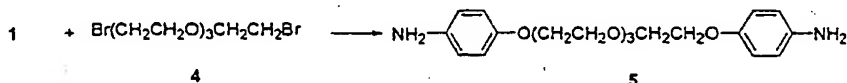
	DMAP	= 4- <i>N,N</i> -dimethylaminopyridine
	DMF	= <i>N,N</i> -dimethylformamide
	DMSO	= dimethylsulfoxide
	DPPA	= diphenylphosphoryl azide
5	g	= gram
	HBTU	= 1-hydroxybenzotriazole
	HPLC	= high performance liquid chromatography
	mg	= milligram
	MIC	= minimum inhibitory concentration
10	min	= minute
	mL	= milliliter
	mm	= millimeter
	mmol	= millimole
	N	= normal
15	PyBOP	= pyridine benzotriazol-1-yloxy-tris(dimethyl-amino)phosphonium hexafluorophosphate
	<i>t</i> -BOC	= <i>tert</i> -butoxycarbonyl
	TBAF	= tetrabutyl ammonium fluoride
	TFA	= trifluoroacetic acid
20	THF	= tetrahydrofuran
	tlc	= thin layer chromatography
	$\mu$ L	= microliters

**Preparation 1: 1,18-di(4-aminophenoxy)octadecane, 3.**



A mixture of 4-aminophenol (0.25 mol), 1,18-dibromooctadecane (0.125 mol), 2,  $\text{K}_2\text{CO}_3$  (25g) and KI (50 mg) in DMF (100 mL) is heated at 90°. The progress of the reaction is monitored by tlc. When it is complete, the solution is cooled and added to water. The aqueous solution is extracted with ether. The extract is dried and evaporated; the residue is chromatographed to afford 3.

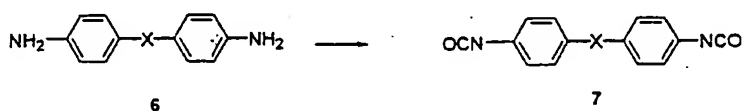
**Preparation 2: 1,11-di(4-aminophenoxy)3,6,9-trioxaundecane, 5.**



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Using the above procedure, but employing 1,11-dibromo-3,6,9-trioxaundecane, 4, in place of 1,18-dibromooctadecane, there is obtained the product 5.

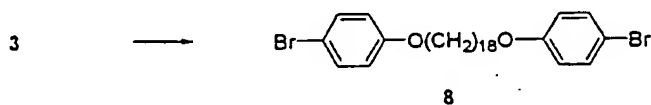
**Preparation 3: 1,4-di(4-isocyanatophenyl)butane, 7, in which X is (CH<sub>2</sub>)<sub>4</sub>.** A.



5            1,4-Di-(4-aminophenyl)butane 6 (0.2 mol) is dissolved in EtOAc (100 mL). Phosgene is bubbled through the EtOAc at 0° until a saturated solution is obtained, and the passage of phosgene is continued for a further hour. The solution is then heated at reflux for two hours, then cooled. A stream of nitrogen is passed through the solution, and it is then filtered. The filtrate is evaporated to afford the  
10            compound 7, in which X is (CH<sub>2</sub>)<sub>4</sub>.

B.        Using the above procedure, but substituting 1,18-di-(4-aminophenoxy)octadecane, 3 or 1,11-di-(4-aminophenoxy)3,6,9-trioxaundecane, 5 for 1,4-(4-aminophenyl)butane, 6, there are obtained respectively the diisocyanates 7, in which X is (CH<sub>2</sub>)<sub>18</sub> or (CH<sub>2</sub>CH<sub>2</sub>O)<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>.

15        **Preparation 4: 1,18-di(4-bromophenoxy)octadecane, 8.**

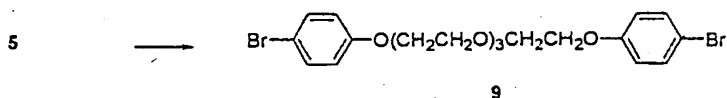


1,18-di(4-aminophenoxy)octadecane, 3, (0.1 mol) is dissolved in concentrated HCl (25 mL) and to the solution is added ice (40 g) and a solution of NaNO<sub>2</sub> (10 g) in water (20 mL). After 1 hour, the excess nitrite is destroyed by the addition of urea, and the solution is filtered. The diazonium chloride solution is

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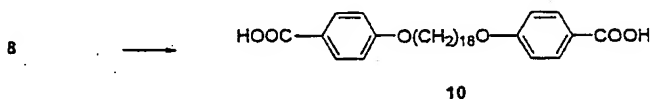
diluted with water (100 mL) and is then added to acetone (400 mL). A solution of CuBr (0.2 mol) and LiBr (0.2 mol) in water (100 mL) is added.. When nitrogen evolution has stopped, the acetone is removed under vacuum and the product is taken up in EtOAc. The EtOAc solution is dried and evaporated, and the residue is  
 5 chromatographed to afford the dibromide 8.

**Preparation 5: 1,11-di(4-bromophenoxy)-3,6,9-trioxaundecane, 9.**



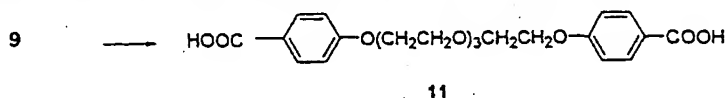
Using the procedure of Preparation 4, but substituting 1,11-di(4-aminophenoxy)-3,6,9-trioxaundecane, 5, for 1,18-di(4-aminophenoxy)octadecane, 3, there is obtained the compound 9.

10 **Preparation 6: 1,18-di(4-carboxyphenoxy)octadecane, 10.**



1,18-Di(4-bromophenoxy)octadecane, 8, (0.1 mol) is dissolved in dry ether (150 mL). The solution is cooled to -78° and n-BuLi in hexane (0.2 mol) is added. After 1 hour, the solution is warmed to room temperature, and is then added rapidly to dry ice (300 g.). The mixture is allowed to warm to room temperature,  
 15 and then dilute HCl is added. The mixture is extracted with EtOAc, and the extract is dried and evaporated and the residue is chromatographed to afford the diacid compound 10.

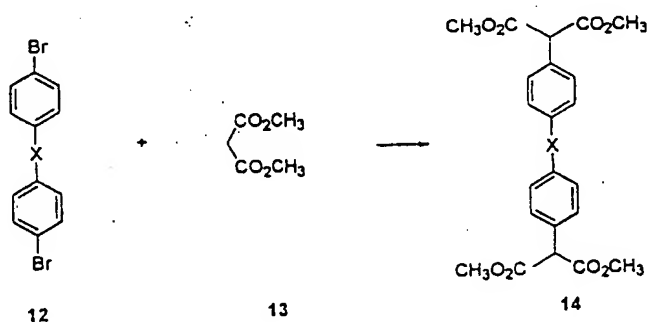
**Preparation 7: 1,11-di(4-carboxyphenoxy)-3,6,9-trioxaundecane, 11.**



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Using the procedure of Preparation 6, but employing 1,11-di-(4-bromophenoxy)-3,6,9-trioxaundecane, 9, in place of 1,18-di-(4-bromophenoxy)octadecane, 8, there is obtained the diacid compound 11.

Preparation 8: 1,4-di-[4-(dicarbomethoxymethyl)phenyl]butane, 14, in which X is (CH<sub>2</sub>)<sub>4</sub>.

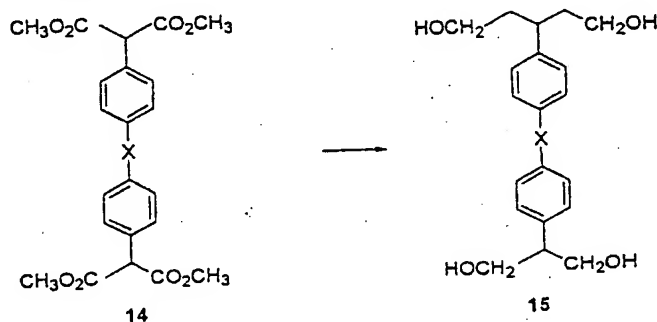


A. Using the procedure described in *Gazz. Chim. Ital.*, 1992, 122, 511, dimethyl malonate (13) (0.2 mol) is dissolved in dioxan (100 mL) and the solution is added dropwise to a suspension of NaH (0.2 mol) in dioxan (100 mL). The temperature is maintained at about 25° by the use of a water bath. When hydrogen evolution has ceased, CuBr (0.06 mol) and 1,4-di-(4-bromophenyl)butane (12) in which X is (CH<sub>2</sub>)<sub>4</sub>, prepared as described in *Quim. Nova*, 1987, 10, 102, (0.1 mol) is added. The mixture is heated at reflux for 4 hours, then the solvent is removed under vacuum. Concentrated HCl (50 mL) is added, and the mixture is extracted with toluene. The extract is washed with dilute NaHCO<sub>3</sub>, then dried and evaporated. The residue is chromatographed to afford the compound 14, in which X is (CH<sub>2</sub>)<sub>4</sub>.

B. Using the above procedure, but substituting 1,18-di-(4-bromophenoxy)octadecane, 8, or 1,11-di-(4-bromophenoxy)-3,6,9-trioxaundecane, 9, for 1,4-di-(4-bromophenyl)butane, 12, there are obtained respectively the compounds 14 in which X is (CH<sub>2</sub>)<sub>18</sub> or (CH<sub>2</sub>CH<sub>2</sub>O)<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>.

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Preparation 9: 1,4-di-[4-(di-(1,3-dihydroxyprop-2-yl)phenyl)]butane, 15, in which X is  $(\text{CH}_2)_4$ .



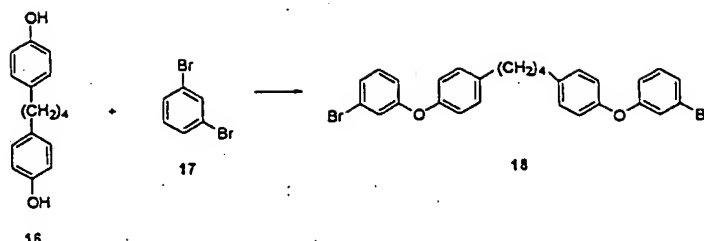
A. Using the procedure described in US Patent 5,091,595, 1,4-di-[4-(dicarbomethoxymethyl)phenyl]butane, 14, in which X is  $(\text{CH}_2)_4$ , (0.05 mol) is dissolved in dry THF (50 mL) and the solution is added slowly to a solution of diisobutylaluminum hydride (0.25 mol) in THF (100 mL) at  $0^\circ$  under nitrogen. After 1 hour, the mixture is warmed to room temperature. After 3 hours, the mixture is cooled to  $0^\circ$  and MeOH (50 mL) then dilute HCl (0.25 mmol) are added. The pH is adjusted to 9-10 by addition of dilute  $\text{K}_2\text{CO}_3$ , and the solution is extracted with EtOAc. The extract is dried and evaporated, and the residue is chromatographed to afford the compound 15, in which X is  $(\text{CH}_2)_4$ .

B. Using the above procedure, but substituting the compounds 14 in which X is  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$  for 14, in which X is  $(\text{CH}_2)_4$ , there are obtained respectively the compounds 15, in which X is  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .

Preparation 10: 1,4-di-[4-(3-bromophenoxy)phenyl]butane, 18.

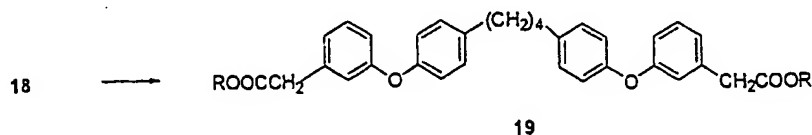


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Using the procedure described in *J. Amer. Chem. Soc.*, 1987, **119**, 10539, 1,3-dibromobenzene, **17**, (0.2 mol) and 1,4-di-(4-hydroxyphenyl)butane, **16**, prepared as described in *Austral. J. Chem.*, 1993, **46**, 277, or European Patent 546639, (0.1 mol) are dissolved in toluene (200 mL) and EtOAc (0.01 mol). To the solution are added  $\text{Cs}_2\text{CO}_3$  (0.4 mol) and copper (I) trifluoromethanesulfonate benzene complex, (0.005 mol). The mixture is heated under reflux and the reaction is monitored by tlc until the reaction is complete. The mixture is cooled and filtered, and the filtrate is evaporated under vacuum. The residue is chromatographed to afford the compound **18**.

- 10 **Preparation 11: 1,4-di-[4-[3-(carboxymethyl)phenoxy]phenyl]butane, 19, in which R is H.**



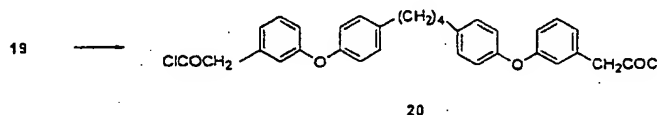
- 15 A. Magnesium (0.2 mol) is placed in a 500 mL round-bottom flask under an inert atmosphere, and dry THF (50 mL) is added. A portion of the solution of the dibromo compound **18** (0.1 mol) in THF (100 mL) and a crystal of iodine are added. When the Grignard reaction has initiated, the remaining amount of the solution of **18** is added, at such a rate as to maintain a gentle reflux. When addition is complete, the solution is allowed to cool, and a solution of anhydrous  $\text{ZnCl}_2$

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(0.2 mol) in dry THF (100 mL) is added. After 2 hours, a solution of methyl bromoacetate (0.2 mol) in dry THF (50 mL) is added. The reaction mixture is heated at reflux for 6 hours, then is cooled and added to dilute HCl. The aqueous mixture is extracted with ether, and the extract is dried and evaporated. The residue is chromatographed to afford the diester product **19**, in which R is methyl.

B. The diester **19** in which R is methyl, (100 mmol) is dissolved in THF (100 mL) and a solution of LiOH, H<sub>2</sub>O (300 mmol) in water (100 mL) is added. The progress of the reaction is monitored by tlc. When it is complete, the mixture is added to dilute HCl and extracted with EtOAc. The extract is dried and evaporated, and the residue is chromatographed to afford the diacid **19**, in which R is H.

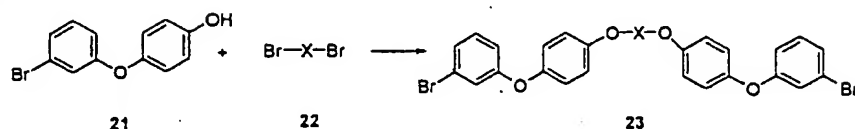
**Preparation 12: 1,4-di-[4-[3-(chlorocarbonylmethyl)phenoxy]phenyl]butane, 20.**



1,4-Di-[4-[3-(carboxymethyl)phenoxy]phenyl]butane, **19**, (0.1 mol) is dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (100 mL). Thionyl chloride (10 mL) and DMF (0.1 mL) are added. After 6 hours, the solvents are removed under vacuum. The residue is redissolved in CH<sub>2</sub>Cl<sub>2</sub> (100 mL), and the solvent is again removed under vacuum to afford the diacid chloride **20**.

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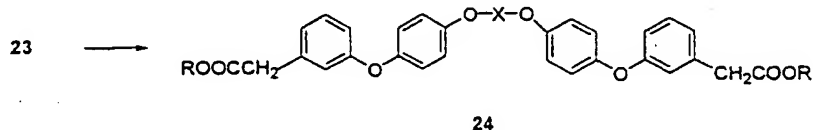
**Preparation 13:** 1,18-di-[4-(3-bromophenoxy)phenoxy]octadecane, 23, in which X is  $(\text{CH}_2)_{18}$ .



A. Using the procedure of Preparation 1, except that 4-(3-bromophenoxy) phenol, 21, prepared as described in *J. Labelled Compds. Radiopharm.*, 1980, 25, 1007, is used in place of 4-aminophenol, 1, there is obtained the compound 23, in which X is  $(\text{CH}_2)_{18}$ .

B. Using the procedure of Preparation 13A, except that 1,11-dibromo-3,6,9-trioxaundecane 9 is used in place of 1,18-dibromooctadecene 22, there is obtained the compound 1,11-di-[4-(3-bromophenoxy)phenoxy]-3,6,9-trioxaundecane 23, in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .

**Preparation 14:** 1,18-di-[4-[3-(carboxymethyl)phenoxy]phenoxy]octadecane, 24, in which X is  $(\text{CH}_2)_{18}$ .

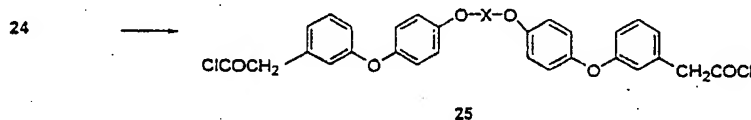


A. Using the procedure of Preparation 11, 1,18-di-[4-(3-bromophenoxy)phenoxy]-octadecane, 23, in which X is  $(\text{CH}_2)_{18}$ , is converted into 24, in which X is  $(\text{CH}_2)_{18}$  and R is H.

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B. Using the procedure of Preparation 11, 1,11-di-[4-(3-bromophenoxy)phenoxy]-3,6,9-trioxaundecane **23**, in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$  is converted into the compound **24**, in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$  and R is H.

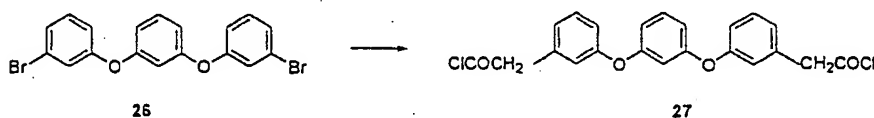
5 Preparation 15: 1,18-di-[4-[3-(chlorocarbonylmethyl)phenoxy]octadecane, **25**, in which X is  $(\text{CH}_2)_{18}$ .



A. Using the procedure of Preparation 12, 1,18-di-[4-[3-(carboxymethyl)phenoxy]phenoxy]octadecane, **24**, in which X is  $(\text{CH}_2)_{18}$  and R is H is converted into **25**, in which X is  $(\text{CH}_2)_{18}$ .

10 B. Using the procedure of Preparation 12, the compound **24**, in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$  and R is H, is converted into the compound **25**, in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .

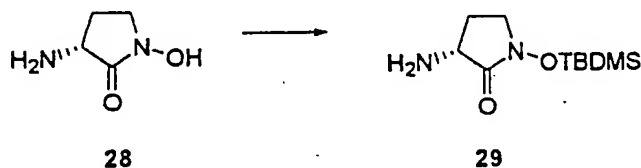
Preparation 16: 1,3-di-[3-(chlorocarbonylmethyl)phenoxy]benzene, **27**.



15 Using the procedures of Preparations 11 and 12, 1,3-di(3-bromophenoxy)benzene, **26**, prepared as described in *Polym. Sci. Technol.*, 1984, **25**, **24**, or US Patent 3,5567,783, is converted into the diacid chloride compound **27**.

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Preparation 17: 3-(R)-amino-1-(tert-butyldimethylsilyloxy)-2-pyrrolidinone, 29.



3-(R)-Amino-1-hydroxy-2-pyrrolidinone, 28 (HA 966) (50 mmol) is dissolved in  $\text{CH}_2\text{Cl}_2$  (50 mL), and triethylamine (250 mmol) and tert-butyldimethylsilyl chloride (55 mmol) are added. The progress of the reaction is monitored by tlc. When it is complete, the solution is washed with water, then dried and evaporated to afford the silylated compound 29.

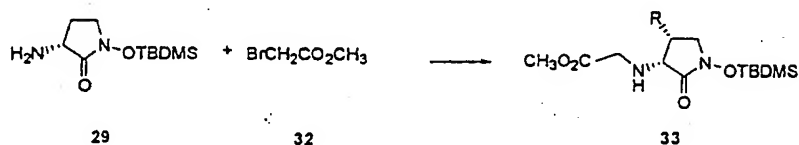
Preparation 18. 3-(R)-amino-1-(tert-butyldimethylsilyloxy)-4-(R)-methyl-2-pyrrolidinone, 31.



Using the procedure of Preparation 17, 3-(R)-amino-1-hydroxy-4-(R)-methyl-2-pyrrolidinone, 30, prepared as described in *Tetrahedron*, 1995, 51, 115821, is converted into the compound 31.

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**Preparation 19.** Alkylation of 3-(R)-amino-1-(tert-butyldimethylsilyloxy)-2-pyrrolidinone, **29**, with methyl bromoacetate, to afford the aminoester **33**, in which R is H.



- A. Methyl bromoacetate, **32**, (50 mmol) and  $K_2CO_3$  (2.0g) are added to a solution of **29** (45 mmol) in DMF (25 mL). The mixture is heated to  $50^\circ$ . The progress of the reaction is monitored by tlc. When it is complete, the solution is cooled and added to water. The aqueous solution is extracted with EtOAc. The extract is dried and evaporated and the residue is chromatographed to afford the compound **33**, in which R is H.

- B. Using the above procedure, but employing the amine **31** in place of **29**, there is obtained the aminoester **33**, in which R is methyl.

**Preparation 20.** Hydrolysis of the aminoester **33** to the acid **34**.



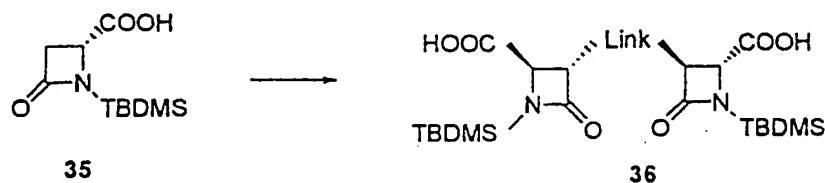
- A. The aminoester **33**, in which R is H, (50 mmol) is dissolved in THF (10 mL) and water (5 mL). A solution of LiOH,  $H_2O$  (55 mmol) in water (5 mL) is added. The progress of the reaction is followed by tlc. When it is complete, the mixture is added to water. The pH is adjusted to 7 by addition of aqueous  $NaH_2PO_4$ , and the solution is extracted with  $CH_2Cl_2$ . The extract is dried and

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evaporated, and the residue is chromatographed to afford the compound **34** in which R is H.

B. Using the above procedure, the aminoester **33**, in which R is methyl, is converted into the compound **34**, in which R is methyl.

- 5 **Preparation 21.** Alkylation of the azetidinone **35** with 1,4-diiodobutane to afford the dimeric product **36**, in which Link is  $(\text{CH}_2)_4$ .



- 10 A solution of lithium diisopropylamide (80 mmol) in THF (50 mL) is added with stirring to a solution of (4R)-N-tert-butyldimethylsilyl-azetidin-2-one-3-carboxylic acid, **35**, prepared as described in *Tetrahedron*, 1990, 46, 4733, (35 mmol) in THF (50 mL) at  $0^\circ$ . After 15 minutes, 1,4-diiodobutane (40 mmol) is added. The progress of the reaction is followed by tlc. When it is complete, the mixture is added to aqueous  $\text{KHSO}_4$  and extracted with EtOAc. The extract is dried and evaporated and the residue is chromatographed to afford the product **36**, in which Link is  $(\text{CH}_2)_4$ .

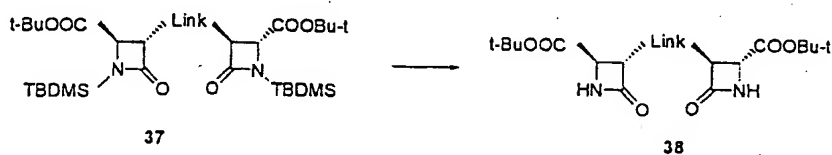
- 15 **Preparation 22:** Conversion of the bis (azetidinone carboxylic acid ) **36** to the corresponding ditertiary butyl ester **37**, in which Link is  $(\text{CH}_2)_4$ .



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The dicarboxylic acid **36**, in which Link is  $(\text{CH}_2)_4$ , (50 mmol) is dissolved in 1:1  $\text{CH}_2\text{Cl}_2$ :cyclohexane (100 mL) and to the solution is added  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  (25 mL) and then tert-butyl trichloroacetimidate (200 mmol). The progress of the reaction is monitored by tlc. When it is complete, solid  $\text{NaHCO}_3$  (20 g) is added and the volatiles are removed under vacuum. The residue is dissolved in  $\text{CH}_2\text{Cl}_2$ , and the solution is washed and dried. The residue is chromatographed to afford the diester **37**, in which Link is  $(\text{CH}_2)_4$ .

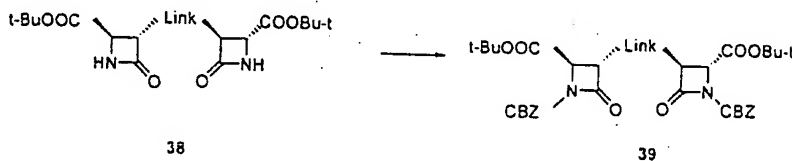
**Preparation 23: Desilylation of the diester **37**, to afford **38**, in which Link is  $(\text{CH}_2)_4$ .**



The diester **37**, in which Link is  $(\text{CH}_2)_4$ , (30 mmol) is dissolved in MeOH (50 mL) and  $\text{CsF}$  (50 mmol) is added. After 3 hours,  $\text{CH}_2\text{Cl}_2$  (100 mL) is added. The mixture is washed with water, then dried and evaporated. The residue is chromatographed to afford the dimeric amide **38**, in which Link is  $(\text{CH}_2)_4$ .

**Preparation 24: Conversion of **38** to the bis-BOC-protected azetidinone **39**, in which Link is  $(\text{CH}_2)_4$ .**

Preparation 24



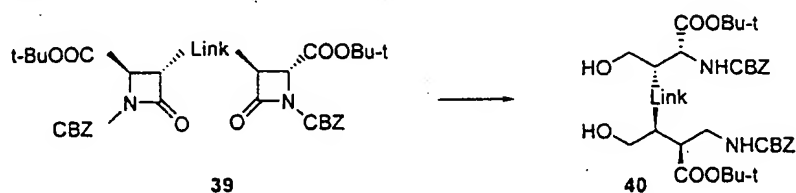
Compound **38**, in which Link is  $(\text{CH}_2)_4$ , (10 mmol) is dissolved in MeCN (50 mL) and *p*-chlorobenzoylchloride (250 mmol) and 4-dimethylaminopyridine (3 mmol) are added. The progress of the reaction is monitored by tlc. When it is



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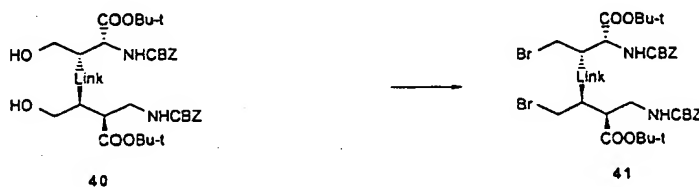
complete, the mixture is diluted with  $\text{CH}_2\text{Cl}_2$  (100 mL). The solution is washed with dilute  $\text{KHSO}_4$ , then dried and evaporated. The residue is chromatographed to afford compound 39, in which Link is  $(\text{CH}_2)_4$ .

**Preparation 25: Reductive ring-opening of the azetidinone 39 to afford the diol 40, in which Link is  $(\text{CH}_2)_4$ .**

**Preparation 25**

The azetidinone 39, in which Link is  $(\text{CH}_2)_4$ , (5 mmol) is dissolved in MeOH (25 mL) at  $0^\circ$ , and  $\text{NaBH}_4$  (15 mmol) is added. The progress of the reaction is monitored by tlc. When it is complete, silica gel (20 g) is added, the mixture is filtered and the solvent is removed under vacuum. The residue is chromatographed to afford the diol 40, in which Link is  $(\text{CH}_2)_4$ .

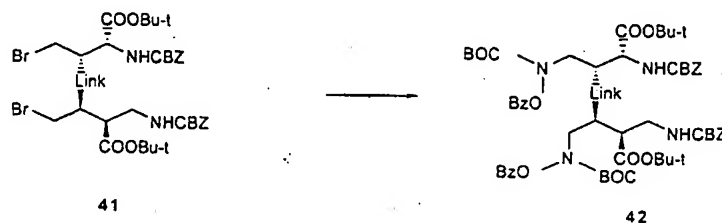
**Preparation 26: Conversion of the diol 40 to the dibromide 41, in which Link is  $(\text{CH}_2)_4$ .**

**Preparation 26**

The diol 40, in which Link is  $(\text{CH}_2)_4$ , (5 mmol) is dissolved in  $\text{CH}_2\text{Cl}_2$  (10 mL) at  $0^\circ$ , and  $\text{CBr}_4$  (12 mmol) is added. A solution of  $\text{PPh}_3$  (15 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL) is added. The progress of the reaction is monitored by tlc. When it is complete, the solvent is removed under vacuum, and the residue is chromatographed to afford the dibromide 41, in which Link is  $(\text{CH}_2)_4$ .

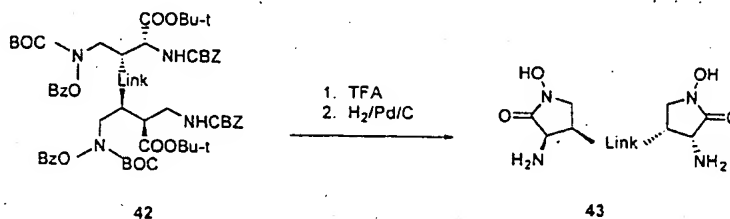
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**Preparation 27:** Displacement reaction of the dibromide **41** with BOCNHOCH<sub>2</sub>Ph to afford the amino product **42**, in which Link is (CH<sub>2</sub>)<sub>4</sub>.

**Preparation 27**

The dibromo compound **41**, in which Link is (CH<sub>2</sub>)<sub>4</sub>, (1 mmol) is dissolved in DMF (10 mL), and K<sub>2</sub>CO<sub>3</sub> (2 mmol), KI (0.02 mmol) and BOCNHOCH<sub>2</sub>Ph (8 mmol) are added to the solution. The progress of the reaction is monitored by tlc. When it is complete, the mixture is diluted with water and extracted with ether. The extract is dried and evaporated, and the residue is chromatographed to afford the compound **42**, in which Link is (CH<sub>2</sub>)<sub>4</sub>.

**Preparation 28:** Deprotection and cyclization of the ditertiary butyl ester **42**, to afford the bis-(pyrrolidinone) **43**, in which Link is (CH<sub>2</sub>)<sub>4</sub>.

**Preparation 28**

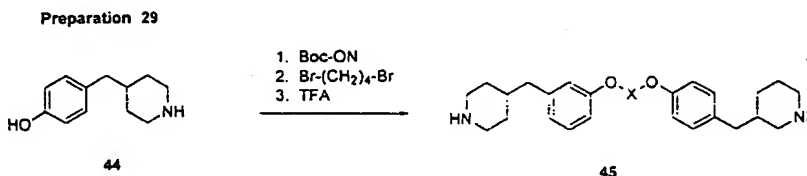
A. Compound **42**, in which Link is (CH<sub>2</sub>)<sub>4</sub>, (1 mmol) is dissolved in TFA (10 mL). The progress of the reaction is monitored by tlc. When it is complete, the TFA is removed under vacuum. The residue is dissolved in methanol, treated with 10% Pd/C, and hydrogenated at 40 psi H<sub>2</sub> for 24 hours. The mixture is filtered through a pad of celite and the filtrate is concentrated under reduced pressure.

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The residue is chromatographed to afford the compound **43**, in which Link is  $(\text{CH}_2)_4$ .

- B. Using the procedures of Preparations 21-28, but employing in Preparation 21 different dialkylating agents, as described herein, in place of 1,4-diiodobutane, there are obtained different bis-(pyrrolidinones) **43**, for example those in which Link is  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .

**Preparation 29: Dialkylation of 1,4-dibromobutane with 4-(4-hydroxybenzyl)piperidine, **44** to yield diether **45**.**



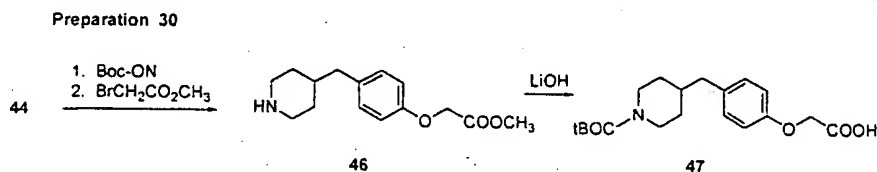
- A. 4-(4-Hydroxybenzyl)piperidine, prepared as described in Oyo Yakuri, 1975, 10, 841-8. (0.2 mol) is dissolved in  $\text{CH}_2\text{Cl}_2$  (200 mL) BOC-ON= $\text{C}(\text{CN})\text{Ph}$ , obtained from the Aldrich Chemical Co., (0.22 mol) and  $\text{Et}_3\text{N}$  (0.50 mol) are added and the progress of the reaction is monitored by tlc. When it is complete, the solution is washed with dilute HCl, then dried and evaporated to afford crude Boc 4-(4-hydroxybenzyl)piperidine, which is purified by chromatography.
- B. Boc 4-(4-hydroxybenzyl)piperidine (0.1 mol) is dissolved in DMF (50 mL) containing  $\text{K}_2\text{CO}_3$  (2.5 g) KI (50 mg) and 1,4-dibromobutane (0.05 mol). The mixture is stirred and the progress of the reaction is monitored by tlc. When it is complete, the mixture is added to water and extracted with EtOAc. The extract is washed, dried and evaporated, and the residue is chromatographed to afford the di-Boc protected form of diether **45**, in which X is  $(\text{CH}_2)_4$ :

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C. Di-Boc **45** (1 mmol) is dissolved in TFA (10 mL). The progress of the reaction is monitored by tlc. When it is complete, the TFA is removed under vacuum, the residue is chromatographed to afford the compound **45**, in which X is  $(\text{CH}_2)_4$ .

5 D. In a similar manner, by employing different dialkylating agents, as described herein, such as 1,18-dibromooctadecane or 1,11-dibromo-3,6,9-trioxaundecane, in place of 1,4-dibromobutane, there are obtained the compounds **45** in which X is  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .

10 Preparation 30: Alkylation of 4-(4-hydroxybenzyl)piperidine, **44**, with methyl bromoacetate, and N-protection and ester hydrolysis of the product, to afford the acid **47**.



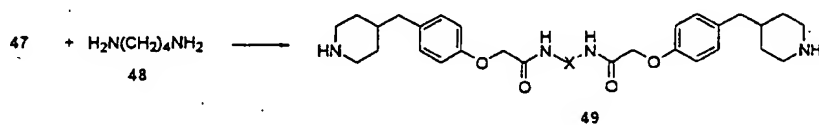
A. 4-Hydroxybenzyl)piperidine (0.2 mol) is dissolved in  $\text{CH}_2\text{Cl}_2$  (200 mL) BOC-ON= $\text{C}(\text{CN})\text{Ph}$ , obtained from the Aldrich Chemical Co., (0.22 mol) and  $\text{Et}_3\text{N}$  (0.50 mol) are added and the progress of the reaction is monitored by tlc.  
 15 When it is complete, the solution is washed with dilute HCl, then dried and evaporated. Boc 4-hydroxybenzyl)piperidine is purified by chromatography.

B. Boc 4-hydroxybenzyl)piperidine (0.1 mol) is dissolved in DMF (50 mL) and  $\text{K}_2\text{CO}_3$  (5 g) and methyl bromoacetate (0.1 mol) are added. The mixture is stirred and the progress of the reaction is monitored by tlc. When it is complete,  
 20 the mixture is added to water and extracted with EtOAc. The extract is washed, dried and evaporated, and the residue is chromatographed too afford the

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intermediate compound 46. The residue is dissolved in THF (100 mL) and a solution of LiOH, H<sub>2</sub>O (0.11 mol) in water (100 mL) is added. The mixture is stirred and the progress of the reaction is monitored by tlc. When it is complete, the mixture is added to dilute HCl and extracted with EtOAc. The extract is washed, dried and evaporated, and the residue is chromatographed to afford the Boc protected acetic acid compound 47.

**Preparation 31: Acylation of 1,4-diaminobutane, 48, with the acetic acid 47, and removal of the BOC group to afford the intermediate 49, in which X is (CH<sub>2</sub>)<sub>4</sub>.**

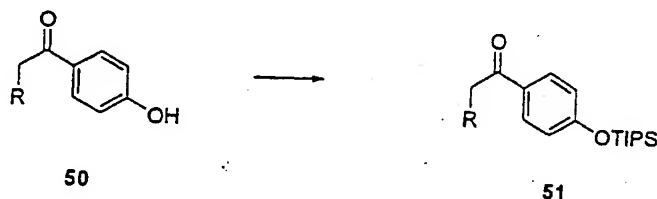


- 10 A. The acetic acid 47 (50 mmol) and dicyclohexylcarbodiimide (50 mmol) are dissolved in CH<sub>2</sub>Cl<sub>2</sub> (100 mL), and 1,4-diaminobutane, 48, (25 mmol) is added. The progress of the reaction is monitored by tlc. When it is complete, the solution is washed with dilute HCl, then dried and evaporated. The residue is dissolved in 3M HCl in EtOAc (50 mL). After 30 minutes the solvent is removed under
- 15 vacuum and the residue is chromatographed to afford the compound 49, in which X is (CH<sub>2</sub>)<sub>4</sub>.

B. Using the above procedure, but employing other diamines as described herein in place of 1,4-diaminobutane, there are obtained the corresponding compounds of the general structure 49.

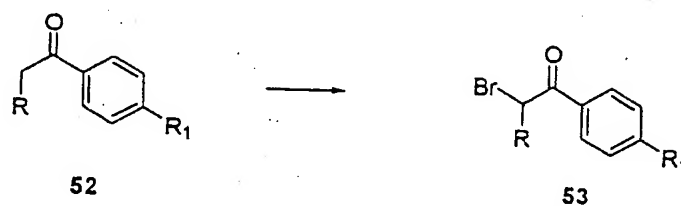
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**Preparation 32:** Silylation of 4-hydroxypropiophenone, 50, to afford 4-triisopropylsilyloxyacetophenone, 51, in which R is methyl.



4-Hydroxypropiophenone, 50, when R is methyl, (0.1 mol) is dissolved in DMF (50 mL) and Et<sub>3</sub>N (0.11 mol) and chlorotriisopropylsilane (0.11 mol) are added. The mixture is stirred and the progress of the reaction is monitored by tlc. When it is complete, the mixture is added to water and extracted with EtOAc. The extract is washed, dried and evaporated, and the residue is chromatographed to afford the intermediate compound 51 in which R is methyl.

**Preparation 33:** Bromination of acetophenones and propiophenones to afford the bromoketones 53.

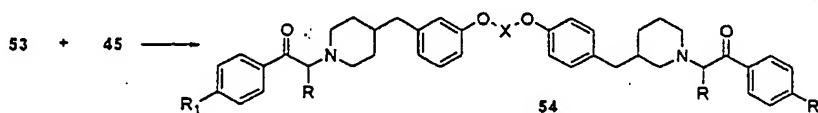


A. Compound 52 in which R is methyl and R<sub>1</sub> is triisopropylsilyloxy (0.1 mol) is dissolved in CCl<sub>4</sub> (100 mL) and the solution is heated to reflux. Bromine (0.1 mol) is added at such a rate that it is absorbed immediately. The solution is cooled and the solvent is removed under vacuum to afford the product 53, in which R is methyl and R<sub>1</sub> is triisopropylsilyloxy.

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B. Using the above procedure. 4-chloroacetophenone, **52**, in which R is H and R<sub>1</sub> is Cl is converted into **53** in which R is H and R<sub>1</sub> is Cl.

**Preparation 34: Alkylation of bromoacetophenones **53** with dimeric piperidine derivatives **45**, to afford the intermediate compounds **54**.**

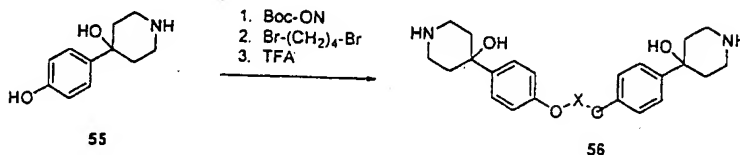


- 5 A. The  $\alpha$ -bromopropiophenone **53** in which R is methyl and R<sub>1</sub> is triisopropylsilyloxy (50 mmol), the piperidine **45**, in which X is (CH<sub>2</sub>)<sub>4</sub>, (25 mmol) and Et<sub>3</sub>N (100 mmol) are dissolved in EtOH (50 mL). The solution is heated under reflux. The progress of the reaction is monitored by tlc. When it is complete, the mixture is added to water and extracted with EtOAc. The extract is
- 10 dried and evaporated and the residue is chromatographed to afford the compound **54**, in which X is (CH<sub>2</sub>)<sub>4</sub>, R is methyl and R<sub>1</sub> is triisopropylsilyloxy.
- B. Using the same procedure.  $\alpha$ -bromo-4-chloroacetophenone **53**, in which R is H and R<sub>1</sub> is Cl, is reacted with the piperidine **45**, in which X is (CH<sub>2</sub>)<sub>4</sub>, to afford the intermediate compound **54**, in which X is (CH<sub>2</sub>)<sub>4</sub>, R is H and R<sub>1</sub> is Cl.
- 15 C. Using the procedures of A and B above, but employing piperidines **45** in which X is (CH<sub>2</sub>)<sub>18</sub> or (CH<sub>2</sub>CH<sub>2</sub>O)<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>, there are obtained the corresponding compounds **54** in which X is (CH<sub>2</sub>)<sub>18</sub> or (CH<sub>2</sub>CH<sub>2</sub>O)<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>.

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**Preparation 35: Alkylation of 1,4-dibromobutane to afford the diether 56, in which X is  $(\text{CH}_2)_4$ .**

Preparation 35



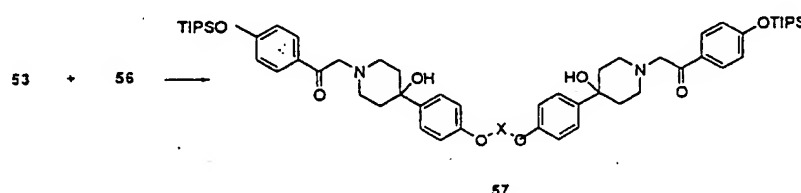
- A. 4-(4-hydroxyphenyl)-4-hydroxypiperidine **55**, prepared as described in European Patent 474561 (0.2 mol) is dissolved in  $\text{CH}_2\text{Cl}_2$  (200 mL) BOC-ON= $\text{C}(\text{CN})\text{Ph}$ , obtained from the Aldrich Chemical Co., (0.22 mol) and  $\text{Et}_3\text{N}$  (0.50 mol) are added and the progress of the reaction is monitored by tlc. When it is complete, the solution is washed with dilute HCl, then dried and evaporated. Boc 4-(4-hydroxyphenyl)-4-hydroxypiperidine is purified by chromatography.
- B. Boc 4-(4-hydroxyphenyl)-4-hydroxypiperidine (100 mmol) is added to DMF (100 mL) containing  $\text{K}_2\text{CO}_3$  (5 g), KI (50 mg) and 1,4-dibromobutane (55 mmol). The mixture is stirred and the progress of the reaction is monitored by tlc. When it is complete, the mixture is added to water and extracted with EtOAc. The extract is washed, dried and evaporated, and the residue is chromatographed to afford the di-Boc protected form of compound **56**, in which X is  $(\text{CH}_2)_4$ .
- C. Di-Boc **56** (1 mmol) is dissolved in TFA (10 mL). The progress of the reaction is monitored by tlc. When it is complete, the TFA is removed under vacuum, and the residue is chromatographed to afford the compound **56**, in which X is  $(\text{CH}_2)_4$ .
- D. Using the above procedure, but employing different dialkylating agents, as described herein, in place of 1,4-dibromobutane, there are obtained the



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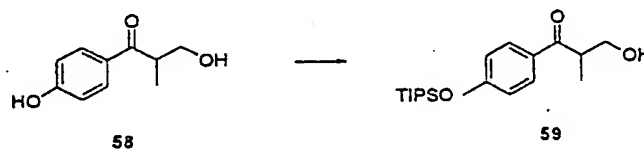
corresponding compounds 56, for example in which X is  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .

**Preparation 36: Reaction between the hydroxypiperidine compound 56 and the bromoketone 53 to afford the dimeric intermediate 57, in which X is  $(\text{CH}_2)_4$ .**



- 5 A. Using the procedure of Preparation 34A, but employing the bromoketone 53 in which R is H and  $R_1$  is triisopropylsilyloxy, and the piperidine 56 in which X is  $(\text{CH}_2)_4$ , there is obtained the dimeric intermediate compound 57, in which X is  $(\text{CH}_2)_4$ .
- B. Using the above procedure, but employing compounds 56 in which X is  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ , there are obtained the corresponding
- 10 compounds 57 in which X is  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .

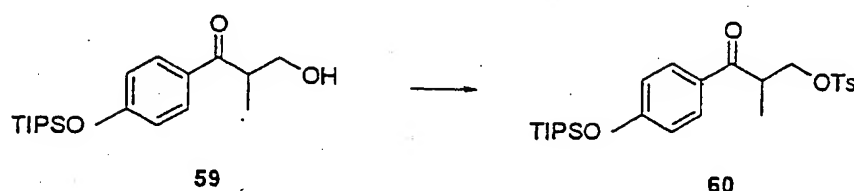
**Preparation 37: Silylation of 3',4-dihydroxy-2'-methylpropiophenone, 58, to afford the intermediate compound 59.**



- Using the procedure of Preparation 32, 3',4-dihydroxy-2'-
- 15 methylpropiophenone, 58, prepared as described in *Synthesis*, 1984, 4, 339-42, is converted into the silyl ether 59.

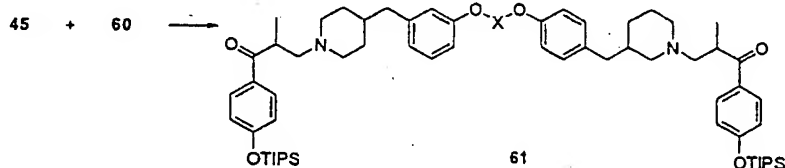
-112-

**Preparation 38: Tosylation of the silyl ether 59 to afford the compound 60.**



The alcohol **59** (100 mmol) is dissolved in pyridine (50 mL) and *p*-toluenesulfonyl chloride (105 mmol) is added. The mixture is stirred and the progress of the reaction is monitored by tlc. When it is complete, the mixture is added to water and extracted with EtOAc. The extract is washed with dilute HCl, then dried and evaporated to afford the toluenesulfonate compound **60**.

**Preparation 39: Alkylation of the toluenesulfonate 60 with the piperidine 45, to afford the dimeric intermediate 61, in which X is (CH<sub>2</sub>)<sub>4</sub>.**

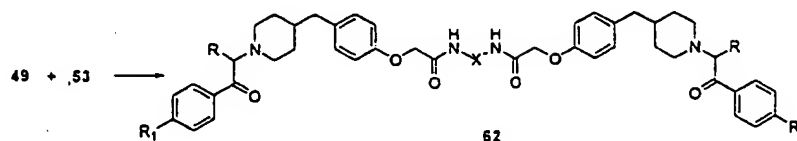


A. The dimeric piperidine **45**, in which X is (CH<sub>2</sub>)<sub>4</sub> (50 mmol) is dissolved in DMF (50 mL) containing K<sub>2</sub>CO<sub>3</sub> (5 g), and the tosylate ester **60** (100 mmol) is added. The progress of the reaction is monitored by tlc. When it is complete, the mixture is added to water and extracted with EtOAc. The extract is washed with dilute HCl, then dried and evaporated. The residue is chromatographed to afford the compound **61**, in which X is (CH<sub>2</sub>)<sub>4</sub>.

B. Using the above procedure, but employing the piperidine compounds **45** in which X is (CH<sub>2</sub>)<sub>18</sub> or (CH<sub>2</sub>CH<sub>2</sub>O)<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>, there are obtained the corresponding compounds **61**, in which X is (CH<sub>2</sub>)<sub>18</sub> or (CH<sub>2</sub>CH<sub>2</sub>O)<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>.

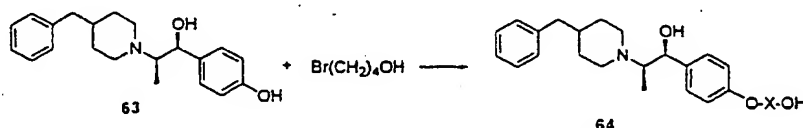
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**Preparation 40:** Alkylation of the amide-linked piperidine intermediate **49** to afford the compound **62** in which X is  $(\text{CH}_2)_4$ .



- A. Using the procedure of Preparation 34, the bromoketones **53**, in which R is H or methyl and  $R_1$  is triisopropylsilyloxy or chloro, are reacted with the piperidine **49** in which X is  $(\text{CH}_2)_4$ , to afford the compounds **62**, in which X is  $(\text{CH}_2)_4$ , R is H or methyl, and  $R_1$  is triisopropylsilyloxy or chloro.
- B. Using the above procedure, but employing the piperidine compounds **49** in which X is  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ , there are obtained the corresponding compounds **62** in which X is  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ , R is H or methyl, and  $R_1$  is chloro or triisopropylsilyloxy.

**Preparation 41:** Alkylation of Ifenprodil, **63**, with 4-bromobutanol, to afford the alcohol **64** in which X is  $(\text{CH}_2)_4$ .



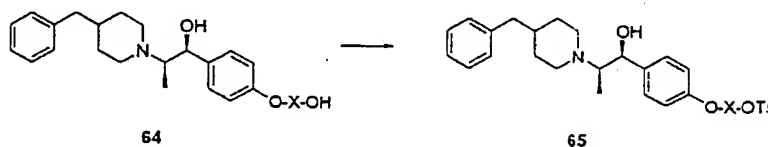
- A. Using the conditions of Preparation 1, Ifenprodil, **63**, prepared as described in *J. Med. Chem.*, 1995, 38, 3138, and 4-bromobutanol are reacted together to afford the alcohol **64**, in which X is  $(\text{CH}_2)_4$ .
- B. Using the above procedure, but employing different bromo alcohols, as described herein, such as 18-bromooctadecanol, or 1-bromo-11-hydroxy-3,6,9-

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trioxaundecane, there are obtained the corresponding compounds **64** in which X is  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .

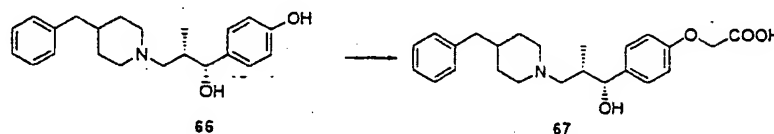
- C. Using the above procedures, but employing, for example, RO-25-6981, **66**, prepared as described in Canadian Patent 2129771, or Nyldrin (**104**), prepared as described in German Patent DE 3037163, or CP-101606, (**102**) prepared as described in *J. Med. Chem.*, 1995, 38, 3138-45, there are obtained the alkylated products analogous to **64**.

**Preparation 42: Conversion of the alcohol **64**, in which X is  $(\text{CH}_2)_4$ , to the tosylate **65**, in which X is  $(\text{CH}_2)_4$ .**



- A. Using the conditions of Preparation 38, the alcohol **64**, in which X is  $(\text{CH}_2)_4$ , is converted into the tosylate **65**, in which X is  $(\text{CH}_2)_4$ .
- B. Using the above conditions, the alcohols whose preparations are described in Preparation 41B and 41C are converted into the corresponding tosylates.

- Preparation 43: Alkylation of RO-25-6981, **66**, with methyl bromoacetate, and hydrolysis of the product to afford the phenoxyacetic acid **67**.**

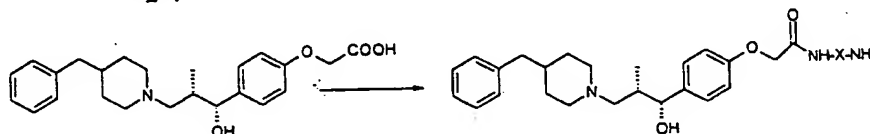


- A. Using the conditions of Preparation 30, RO-25-6981, **66**, is converted into the acid **67**.

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B. Using the above conditions, Ifenprodil, (63) Nyldrin (104) or CP-101606 (102) or the like are converted into the analogous phenoxyacetic acids.

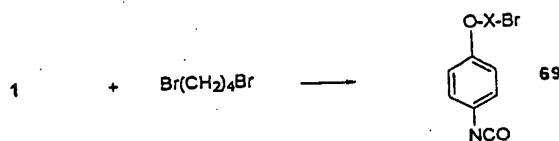
**Preparation 44: Amination of the acetic acid 67 to afford the amide 68, in which X is  $(CH_2)_4$ .**



- 5 A. The acetic acid 67, in which X is  $(CH_2)_4$  (100 mmol) is dissolved in DMF (100 mL) and dicyclohexylcarbodiimide (100 mmol) is added, followed by 1,4-diaminobutane (500 mmol). The progress of the reaction is followed by tlc. When it is complete, the mixture is added to water and extracted with EtOAc. The extract is dried and evaporated and the residue is chromatographed to afford the
- 10 aminoamide 68, in which X is  $(CH_2)_4$ .
  
- B. Using the same procedure, but employing different aminoalcohols, such as 18-aminooctadecanol, or 1-amino-11-hydroxy-3,6,9-trioxaundecane, there are obtained the corresponding compounds 68 in which X is  $(CH_2)_{18}$  or  $(CH_2CH_2O)_3CH_2CH_2$ .
  
- 15 C. Using the procedures A and B above, but employing as starting materials the phenoxyacetic acids described in Preparation 43B, the analogous aminoamides are obtained.

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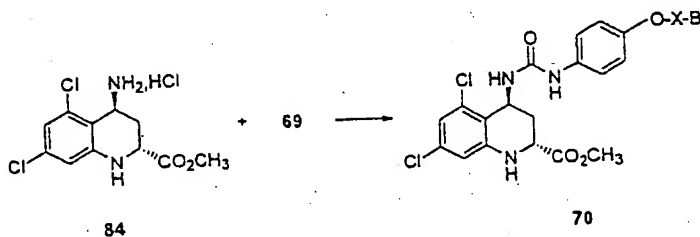
Preparation 45: 1-bromo-4-(4-isocyanatophenoxy)butane, **69**, in which X is  $(\text{CH}_2)_4$ .



A. Using the conditions of preparation 1, equimolar amounts of **1** and 1,4-dibromobutane are reacted to afford after chromatography 4-(4-aminophenoxy)-1-bromobutane. This compound is treated under the conditions of Preparation 3 to afford the isocyanate **69**, in which X is  $(\text{CH}_2)_4$ .

B. In a similar manner, the compounds **69** in which X is  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$  are prepared.

Preparation 46: Reaction of the isocyanate **69** with the 4-aminotetrahydroquinoline **84** to afford the urea intermediate **70** in which X is  $(\text{CH}_2)_4$ .

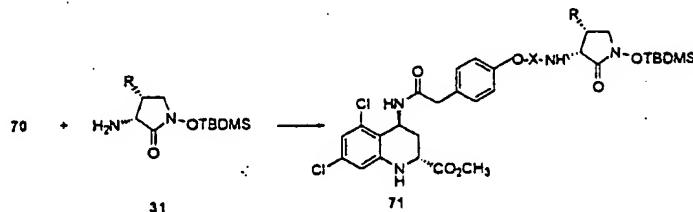


A. Using the conditions of Example 1A, the isocyanate **69** is reacted with the amine **84** to afford the urea **70** in which X is  $(\text{CH}_2)_4$ .

B. In a similar manner, the products of Preparation 45B are converted into the ureas **70** in which X is  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .

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**Preparation 47: Alkylation of the bromo compound 70 with amines derived from HA-966 and L-687414, 31, to give the intermediate 71 in which X is  $(CH_2)_4$ .**



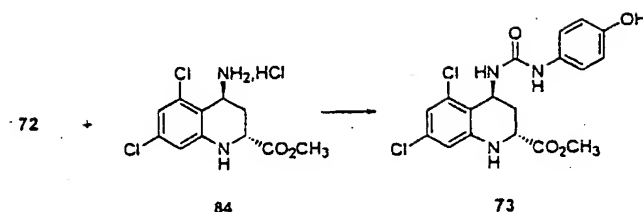
- A. Using the conditions of Preparation 29, the silyl-protected amine 31, in which R is H, is reacted with the bromo compound 70, to afford the amine 71, in which X is  $(CH_2)_4$  and R is H.
- B. Using the above conditions, but employing the bromo compounds 70 in which X is  $(CH_2)_{18}$  or  $(CH_2CH_2O)_3CH_2CH_2$ , there are obtained the corresponding compounds 71 in which X is  $(CH_2)_{18}$  or  $(CH_2CH_2O)_3CH_2CH_2$ .
- C. Using the conditions of A and B above, but employing the amine 31 in which R is methyl, there are obtained the compounds 71 in which R is methyl.

**Preparation 48: 1-tert-butyldimethylsilyloxy-4-isocyanatobenzene, 72.**



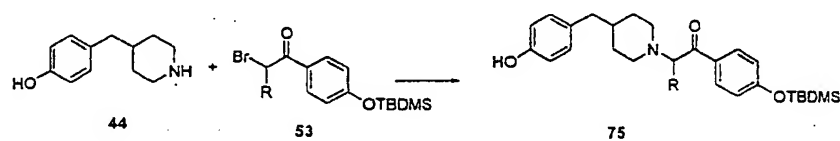
Using the procedure of Preparation 17, followed by the procedure of Preparation 3, 4-aminophenol, 1, is converted into the compound 72.

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**Preparation 49: 4-hydroxyphenylurea 73.**

Using the procedure of Example 1, the isocyanate 72 is reacted with the amine 84 to afford the silyl-protected ureas. This material is dissolved in THF, and Bu<sub>4</sub>NF (2 mole eq) in THF is added. After 1 hour, the mixture is added to water and extracted with EtOAc. The extract is dried and evaporated to afford the compound 73.

**Preparation 50: Reaction of the bromoketone 53, in which R is methyl, with 4-(4-hydroxybenzyl)piperidine, 44, to afford the amine 75, in which R is methyl.**

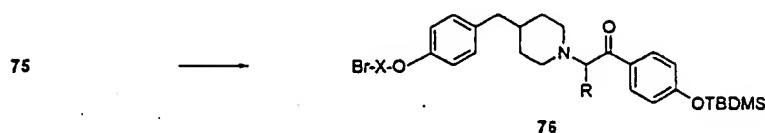


Using the conditions of Preparation 34, 44 and 53 are reacted to produce the amine 75 in which R is methyl.



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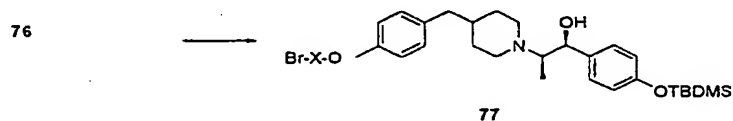
**Preparation 51: Alkylation of the phenol 75 to afford the ether 76, in which X is  $(\text{CH}_2)_4$  and R is methyl.**



A. Using the conditions of Preparation 1, equimolar quantities of the phenol 75 and 1,4-dibromobutane are reacted to afford the ether 76 in which X is  $(\text{CH}_2)_4$  and R is methyl.

B. In a similar manner, by employing  $\text{Br}(\text{CH}_2)_{18}\text{Br}$  or  $\text{Br}(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2\text{Br}$  in place of 1,4-dibromobutane, there are obtained the corresponding compounds 76 in which X is  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .

**Preparation 52: Reduction of the ketone 76, to afford the alcohol 77, in which X is  $(\text{CH}_2)_4$ .**

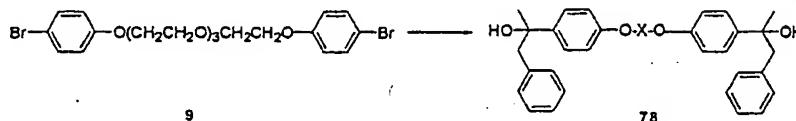


A. Using the procedures of Example 9A, the ketone 76 in which X is  $(\text{CH}_2)_4$  is transformed into the alcohol 77, in which X is  $(\text{CH}_2)_4$ .

B. Using the above procedure, but employing the ketone 76 in which X is  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ , there are obtained the corresponding compounds 77 in which X is  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .

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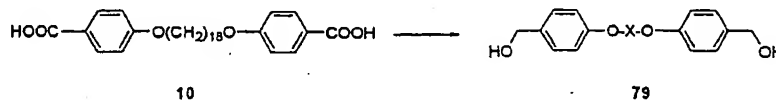
**Preparation 53: Dimeric remacemide intermediate compound 78, in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .**



A. The dibromide 9 ( 50 mmol) is dissolved in dry ether (100 mL) at 0° and n-BuLi in hexane (100 mmol) is added. After 1 hour, a solution of phenylacetone (50 mmol) in dry ether (30 mL) is added. The solution is left for 1 hour, then added to water. The organic solution is washed with dilute HCl, then dried and evaporated. The residue is chromatographed to afford the compound 78 in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .

B. Using the above procedure, but employing 1,4-di-(4-bromophenoxy)butane or the dibromide 8, in place of 9, there are obtained the compounds 78 in which X is  $(\text{CH}_2)_4$  and  $(\text{CH}_2)_{18}$ .

**Preparation 54: Reduction of the diacid 10 to the biscarbinol 79, in which X is  $(\text{CH}_2)_{18}$ .**

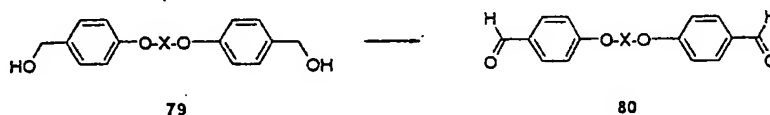


A. The diacid 10 (50 mmol) is dissolved in THF (100 mL) at 0°, and a solution of LAH (100 mmol) in THF (50 mL) is added. The reaction mixture is heated to affect the reaction which is monitored by tlc. When it is complete, the excess LAH is destroyed by addition of aqueous sodium potassium tartrate, and the mixture is then extracted with EtOAc. The extract is dried and evaporated and the residue is chromatographed to afford the compound 79, in which X is  $(\text{CH}_2)_{18}$ .

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B. Using the above procedure, but employing the diacid 1,4-di-(4-carboxyphenyl)butane or the diacid 11 in place of 10, there are obtained the compounds 79 in which X is  $(\text{CH}_2)_4$  and  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .

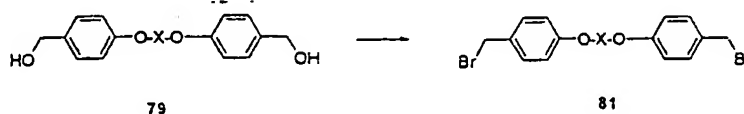
**Preparation 55: Oxidation of the biscarbinol 79 to the dialdehyde 80, in which X is  $(\text{CH}_2)_4$ .**



A. The carbinol 79, in which X is  $(\text{CH}_2)_4$ , (50 mmol) is dissolved in  $\text{CH}_2\text{Cl}_2$  (100 mL). Pyridinium chlorochromate (110 mmol) is added in portions with stirring. The progress of the reaction is monitored by tlc. When it is complete, the solution is filtered through a small plug of silica gel, then evaporated under vacuum. The residue is chromatographed to afford the compound 80, in which X is  $(\text{CH}_2)_4$ .

B. Using the above procedure, but employing the carbinols 79 in which X is  $(\text{CH}_2)_{18}$  and  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ , there are obtained the compounds 80 in which X is  $(\text{CH}_2)_{18}$  and  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .

**Preparation 56: Conversion of the biscarbinol 79, in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ , to the dibromide 81 in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .**

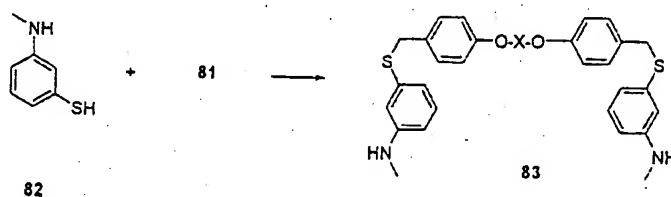


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A. Using the procedure of Preparation 26, the biscarbinol **79** is converted into the dibromide **81** in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .

B. Using the above procedure, but employing the biscarbinols **79** in which X is  $(\text{CH}_2)_4$  or  $(\text{CH}_2)_{18}$ , there are obtained the corresponding dibromides **81**.

5 Preparation 57: Alkylation of the thiol **82** with the dibromide **81** in which X is  $(\text{CH}_2)_{18}$  to afford the thioether **83** in which X is  $(\text{CH}_2)_{18}$ .

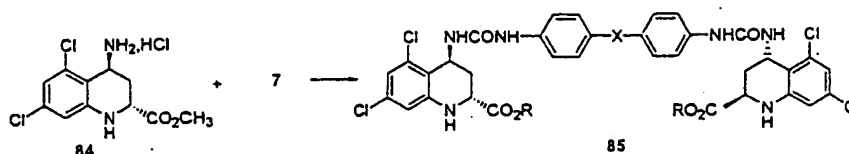


A. A solution of the dibromo compound **81** in which X is  $(\text{CH}_2)_{18}$  (50 mmol) in  $\text{CH}_2\text{Cl}_2$  (50 mL) is added over a period of 2 hours to a solution of the thiol **82**, prepared as described in South African Patent 8502022 or European Patent 123543, (100 mmol) and diisopropylethylamine (200 mmol) in  $\text{CH}_2\text{Cl}_2$  (100 mL) at  $0^\circ$ . The mixture is then left for an additional 3 hours, then the solution is washed with dilute NaOH, dried and evaporated. The residue is chromatographed to afford the compound **83** in which X is  $(\text{CH}_2)_{18}$ .

B. Using the above procedure, but employing the biscarbinols **79** in which X is  $(\text{CH}_2)_4$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ , there are obtained the corresponding dibromides **81**.

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**Example 1: Dimeric urea analogs 85 of L-689560 in which X is  $(\text{CH}_2)_4$ ,  $(\text{CH}_2)_{18}$  and  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$  and R is H.**



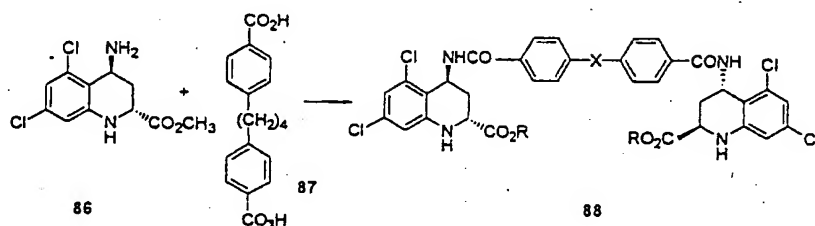
A. Methyl 4-amino-5,7-dichloro-1,2,3,4-tetrahydroquinoline-2-carboxylate hydrochloride, **84**, prepared as described in *J. Med. Chem.*, 1992, 35, 1954, (10 mmol) is suspended in  $\text{CH}_2\text{Cl}_2$  (50 mL), and  $\text{Et}_3\text{N}$  (12.5 mmol) is added. The mixture is stirred until a homogeneous solution is obtained. A solution of the diisocyanate **7** in which X is  $(\text{CH}_2)_4$ , prepared as described in Preparation 3, (5.5 mmol) in  $\text{CH}_2\text{Cl}_2$  (20 mL) is added. The progress of the reaction is monitored by tlc. When it is complete,  $\text{EtOAc}$  (100 mL) is added, and the solution is washed with 1M citric acid, then dried and evaporated. The residue is chromatographed to afford the compound **85** in which X is  $(\text{CH}_2)_4$  and R is methyl.

B. The above compound (5 mmol) is dissolved in THF (20 mL) and  $\text{LiOH}$ ,  $\text{H}_2\text{O}$  (15 mmol) in water (20 mL) is added. The progress of the reaction is monitored by tlc. When it is complete, the mixture is added to water. The pH is adjusted to 7 by addition of aqueous  $\text{NaH}_2\text{PO}_4$ . The mixture is extracted with  $\text{CH}_2\text{Cl}_2$ , and the extract is dried and evaporated. The residue is chromatographed to afford the compound **85** in which X is  $(\text{CH}_2)_4$  and R is H.

C. In a similar manner, by employing the diisocyanates **7**, in which X is  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$  in place of the diisocyanate **7** in which X is  $(\text{CH}_2)_4$ , the corresponding dimeric products **85** in which X is  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$  are obtained.

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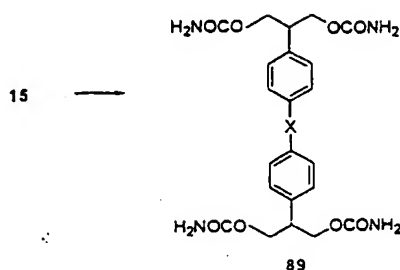
Example 2: Dimeric amide analogs 88 of L-689560 in which X is  $(\text{CH}_2)_4$ ,  $(\text{CH}_2)_{18}$  and  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .



- A. Methyl 4-amino-5,7-dichloro-1,2,3,4-tetrahydroquinoline-2 carboxylate, **86** prepared as described in *J. Med. Chem.*, 1992, 35, 1954, ( 1 mmol) is dissolved in DMF (20 mL). Dicyclohexylcarbodiimide (2.5 mmol) and 1,4-di-(4-carboxyphenyl)butane **87**, prepared as described in US Patent 4,711,900 ( 0.55 mmol) are added. The progress of the reaction is monitored by tlc. When it is complete, the mixture is added to water and extracted with EtOAc. The extract is dried and evaporated and the residue is chromatographed to afford the compound **88**, in which X is  $(\text{CH}_2)_4$  and R is methyl.
- B. In a similar manner, by employing the diacids **10** or **11**, in place of the diacid **87**, the dimeric urea compounds **88**, in which X is  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$  and R is methyl are obtained.
- C. Using the conditions of Example 1B, the compounds **88** in which R is methyl are converted into the compounds **88** in which R is H.

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Example 3: Dimeric analogs 89 of Felbamate in which X is  $(\text{CH}_2)_4$ ,  $(\text{CH}_2)_{18}$  and  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .

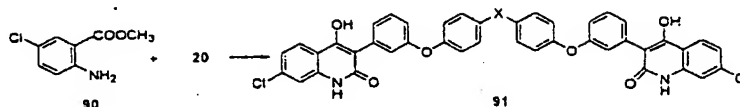


A. Using the procedure described in US Patent 5,091,595, 1,4-di-[4-(di-(1,3-dihydroxyprop-2-yl)phenyl)]butane, 15, in which X is  $(\text{CH}_2)_4$ , obtained as described in Preparation 9, (100 mmol) is dissolved in toluene (100 mL) and THF (30 mL) and phosgene is passed into the solution, with cooling to maintain the temperature at 25°. After 20 g of phosgene has been passed into the solution, the mixture is left for 3 hours. The solution is then added dropwise to concentrated  $\text{NH}_4\text{OH}$  (150 mL) with vigorous agitation. After 1 hour, the solvents are removed under vacuum and the residue is stirred with water (200 mL) for 2 hours. The suspension is then filtered to afford the compound 89 in which X is  $(\text{CH}_2)_4$ .

B. In a similar manner, by employing the dimeric tetrahydroxy compounds 15, in which X is  $(\text{CH}_2)_{18}$  and  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ , prepared as described in Preparation 9, in place of 15 in which X is  $(\text{CH}_2)_4$ , there are obtained the corresponding compounds 89 in which X is  $(\text{CH}_2)_{18}$  and  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .

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Example 4: Dimeric analogs **91** of L-701324, in which X is  $(\text{CH}_2)_4$ ,  $(\text{CH}_2)_{18}$  and  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .



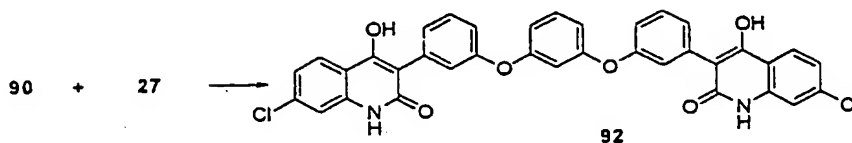
- A. Methyl 5-chloroanthranilate **90** (110 mmol) is dissolved in 1,2-dichloroethane (100 mL) and to the solution is added the di-(phenylacetyl chloride) **20**, the preparation of which is described in Preparation 12 (50 mmol). The mixture is heated to  $80^\circ$ , and the progress of the reaction is monitored by tlc. When it is complete, the solution is cooled and washed with dilute  $\text{Na}_2\text{CO}_3$ , then dried and evaporated. The residue is dissolved in THF (50 mL). The solution is cooled to  $0^\circ$  and a solution of potassium hexamethyldisylazide (200 mmol) in THF (50 mL) is added. The progress of the reaction is monitored by tlc. When it is complete, trifluoroacetic acid (10 mL) is added. The mixture is added to water and extracted with EtOAc. The extract is dried and evaporated, and the residue is chromatographed to afford the compound **91**, in which X is  $(\text{CH}_2)_4$ .

- B. In a similar manner, by employing the di-(phenylacetyl chlorides) **25**, in which X is  $(\text{CH}_2)_{18}$  and  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ , the preparations of which are described in Preparation 16, in place of **20**, there are obtained the corresponding compounds (**91**) in which X is  $(\text{CH}_2)_{18}$  and  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .



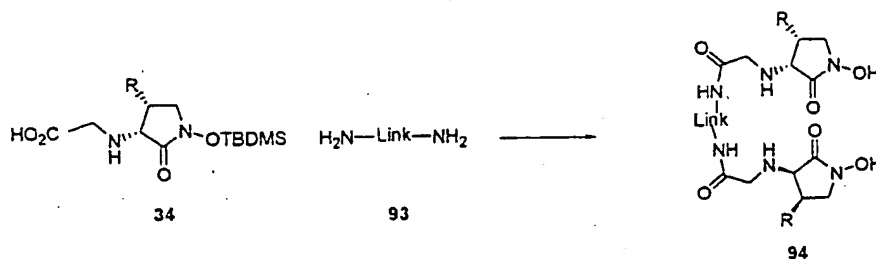
-127-

**Example 5: Dimeric analog 92 of L-701324 in which X is 1,3'-benzendiyl.**



Using the procedures of Example 4A, but employing 1,3-di-[3-(chlorocarbonylmethyl)-phenoxy]benzene, 27, prepared as described in Preparation 16, in place of the di-(phenylacetyl chloride) 20, there is obtained the dimeric compound 92.

**Example 6: Dimeric amide analogs 93 of HA 966 and L-687414, (94).**



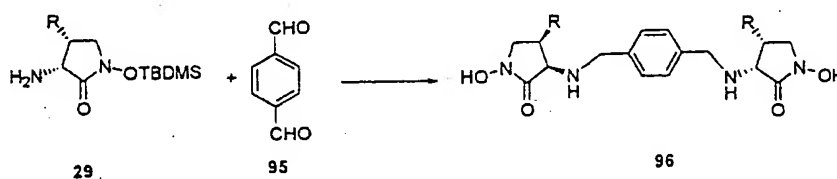
- A. The substituted glycine 34, in which R is H, the preparation of which is described in Preparation 20, (5 mmol) is dissolved in DMF (20 mL) and 1,4-diaminobutane 93 (3 mmol) and dicyclohexylcarbodiimide (6 mmol) are added.
- 10 The progress of the reaction is monitored by tlc. When it is complete, the mixture is added to water and extracted with EtOAc. The extract is dried and evaporated. The residue is dissolved in THF (25 mL) and a solution of Bu<sub>4</sub>NF (5 mmol) in THF is added. The progress of the reaction is monitored by tlc. When it is complete, the mixture is washed with water, then dried and evaporated.
- 15 The residue is chromatographed to afford the diamide compound 94, in which Link is (CH<sub>2</sub>)<sub>4</sub> and R is H.

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B. Using the above procedure, but employing the glycine derivative **34**, in which R is methyl, in place of **34** in which R is H, there is obtained the diamide compound **94** in which Link is  $(CH_2)_4$  and R is methyl.

5 C. Using the procedures of A and B above, but employing different diamines, as described herein, in place of 1,4-diaminobutane, there are obtained the corresponding compounds **94**

**Example 7: Reductive coupling of HA 966 and L-687414 derivatives to afford the dimeric compounds 96**

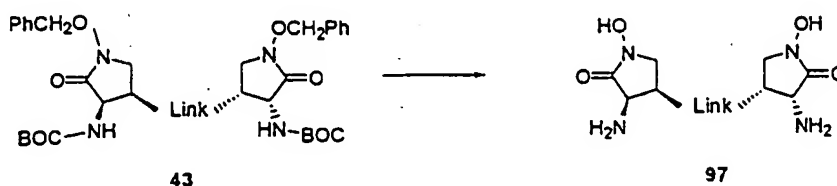


10 A. Using the procedure described in *J. Org. Chem.*, 1985, **49**, 1927,  $NaBH_3CN$  (1 mmol) is dissolved in MeOH (3 mL) and to the solution is added  $ZnCl_2$  (1 mmol). The resulting solution is added to a solution of the amine **29** (1 mmol) and terephthalaldehyde **95**, (0.5 mmol). The progress of the reaction is followed by tlc. When it is complete, the mixture is added to 1M NaOH and extracted with EtOAc. The extract is dried and evaporated, and the residue is  
15 chromatographed to afford the dimeric product **96**.

B. Using the above procedure, but employing different aliphatic or aromatic dialdehydes in place of terephthalaldehyde, there are obtained the dimeric compounds analogous to **96**.

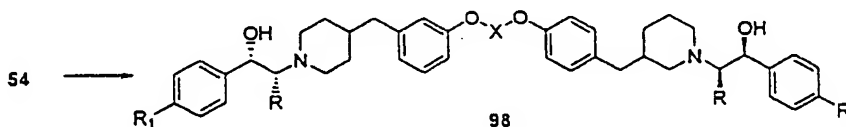
-129-

**Example 8: Deprotection of the dimeric compound 43 to afford the L-687414 dimer 97 in which Link is  $(\text{CH}_2)_4$ .**



- A. The O-benzyl N-BOC protected dimer **43**, in which Link is  $(\text{CH}_2)_4$ , prepared as described in Preparation 28A, (0.5 mmol) is dissolved in MeOH (10 mL).  $\text{Pd}(\text{OH})_2$  (20 mg) is added, and the mixture is stirred under an atmosphere of hydrogen. The progress of the reaction is monitored by tlc. When it is complete, the mixture is filtered and the solvent is removed under vacuum. The residue is chromatographed to afford the compound **97**, in which Link is  $(\text{CH}_2)_4$ .
- B. Using the products described in Preparation 28B, and employing the procedure of Example 8A, there are obtained the corresponding compounds **97**.

**Example 9: Reduction and deprotection of the silyl ketone 54 to afford the dimeric ether-linked Ifenprodil and Eliprodil analogs 98.**



- A. The dimeric ketone **54**, in which X is  $(\text{CH}_2)_4$ , R is methyl and  $\text{R}_1$  is triisopropylsilyloxy, (10 mmol) is dissolved in EtOH (10 mL) and  $\text{NaBH}_4$  (20 mmol) is added. The progress of the reaction is monitored by tlc. When it is complete, the solution is added to water and extracted with EtOAc. The extract is dried and evaporated to afford a residue.

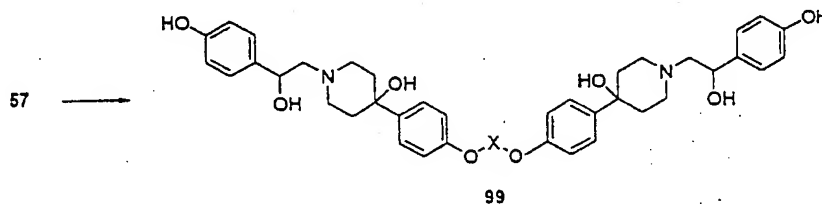
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B. The residue from A is dissolved in THF (10 mL) and a solution of  $\text{Bu}_4\text{NF}$  (15 mmol) in THF (10 mL) is added. After 1 hour, the mixture is added to water and extracted with EtOAc. The extract is dried and evaporated and the residue is chromatographed to afford the compound **98**, in which X is  $(\text{CH}_2)_4$ , R is methyl and  $\text{R}_1$  is OH.

C. Using procedures A and B above, but employing the compounds **54** in which X is  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ , there are obtained the compounds **98** in which X is  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ . R is methyl and  $\text{R}_1$  is OH.

D. Using procedure A above, but employing the compound **54** in which X is  $(\text{CH}_2)_4$ , R is H and  $\text{R}_1$  is Cl, there is obtained a residue which is chromatographed to afford the compound **98** in which X is  $(\text{CH}_2)_4$  and  $\text{R}_1$  is Cl. Alternatively, employing the compound **54** in which X is  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ , R is H and  $\text{R}_1$  is Cl, there is obtained a residue which is chromatographed to afford the compound **98** in which X is  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ , R is H and  $\text{R}_1$  is Cl.

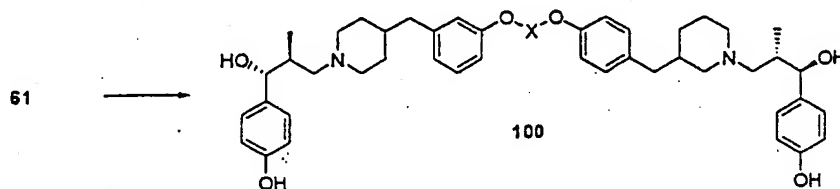
Example 10: Reduction and deprotection of the silyl ketones **57** to afford the dimeric CP-101606 analogs **99**, in which X is  $(\text{CH}_2)_4$ ,  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .



Using the procedures of Examples 9A and 9B, the compounds **57** in which X is  $(\text{CH}_2)_4$ ,  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$  are converted into the compounds **99** in which X is  $(\text{CH}_2)_4$ ,  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .

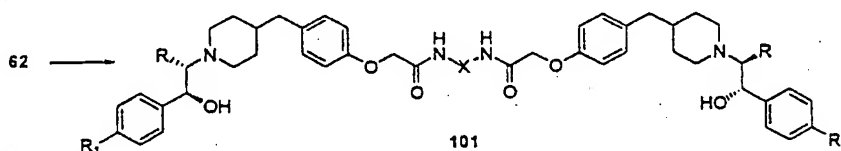
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**Example 11: Reduction and deprotection of the silyl ketones 61, to afford the dimeric RO-25-6981 analogs 100, in which X is  $(CH_2)_4$ ,  $(CH_2)_{18}$  or  $(CH_2CH_2O)_3CH_2CH_2$ .**



Using the procedures of Examples 9A and 9B, the compounds 61, in which  
 5 X is  $(CH_2)_4$ ,  $(CH_2)_{18}$  or  $(CH_2CH_2O)_3CH_2CH_2$ , are converted into the compounds  
 100 in which X is  $(CH_2)_4$ ,  $(CH_2)_{18}$  or  $(CH_2CH_2O)_3CH_2CH_2$ .

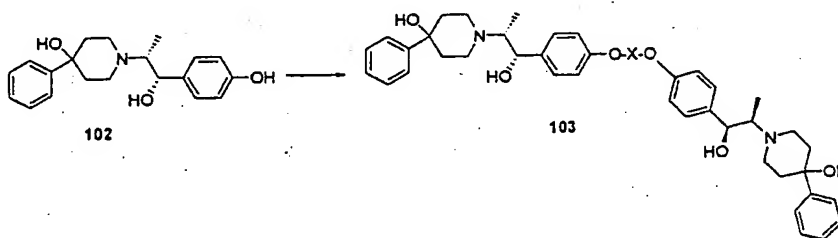
**Example 12: Reduction and deprotection of the silyl ketone 62, to afford the dimeric amide-linked Ifenprodil and Eliprodil analogs 101.**



Using the procedure of Examples 9A and, if appropriate, that of Example  
 10 9B, the compounds 62 in which X is  $(CH_2)_4$ ,  $(CH_2)_{18}$  or  $(CH_2CH_2O)_3CH_2CH_2$ , R is  
 methyl or H, and  $R_1$  is triisopropylsilyloxy or Cl, are converted into the  
 compounds 101, in which X is  $(CH_2)_4$ ,  $(CH_2)_{18}$  or  $(CH_2CH_2O)_3CH_2CH_2$ , R is  
 methyl or H, and  $R_1$  is OH or Cl.

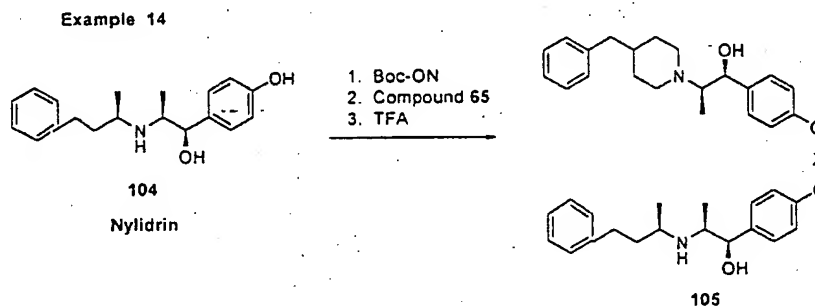
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**Example 13:** Alkylation of CP-101606 (**102**) with 1,11-dibromo-3,6,9-trioxaundecane to afford the dimeric ether (**103**) in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .



- A. Using the conditions of Preparation 2, CP-101606, **102**, is converted into the dimeric ether **103** in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .
- B. Using the above conditions, but employing different dialkylating agents, as described herein, for example 1,4-dibromobutane or 1,18-dibromooctadecane, in place of 1,11-dibromo-3,6,9-trioxaundecane, there are obtained the corresponding compounds **103** in which X is  $(\text{CH}_2)_4$  or  $(\text{CH}_2)_{18}$ .
- C. Using the above conditions, but employing different phenolic starting materials in place of CP-101606, such as Ifenprodil **63** or RO-25-6981 **66**, the corresponding dimeric ethers are obtained.

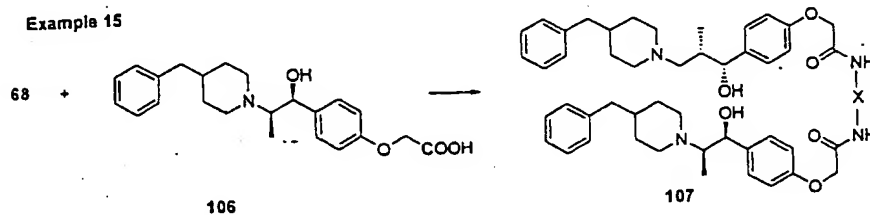
**Example 14:** Alkylation of Nyldrin (**104**), with the Ifenprodil tosylate **65**, to afford the heterodimeric ether **105** in which X is  $(\text{CH}_2)_4$ .



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- A. Nylidrin **104** (0.2 mol) is dissolved in  $\text{CH}_2\text{Cl}_2$  (200 mL). BOC-  
 $\text{ON}=\text{C}(\text{CN})\text{Ph}$ , obtained from the Aldrich Chemical Co., (0.22 mol) and  $\text{Et}_3\text{N}$   
 (0.50 mol) are added and the progress of the reaction is monitored by tlc. When it  
 is complete, the solution is washed with dilute HCl, then dried and evaporated.
- 5 Boc Nylidrin is purified by chromatography.
- B. Using the conditions of Preparation 1, equimolar amounts of Boc Nylidrin  
 and the tosylate **65** are reacted together to afford the di-Boc protected form of  
 dimeric ether **105** in which X is  $(\text{CH}_2)_4$ .
- C. Di-Boc **105** (1 mmol) is dissolved in TFA (10 mL). The progress of the  
 10 reaction is monitored by tlc. When it is complete, the TFA is removed under  
 vacuum, and the residue is chromatographed to afford the compound **105**, in which  
 X is  $(\text{CH}_2)_4$ .
- D. Using the above conditions, but employing the tosylates **65** in which X is  
 $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$  or  $(\text{CH}_2)_{18}$  the corresponding dimeric ethers **105** in which X  
 15 is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$  or  $(\text{CH}_2)_{18}$  are obtained.

**Example 15: Amide formation between the amine 68, derived from RO-25-  
 6981, and the oxyacetic acid 106 derived from Ifenprodil to afford the  
 heterodimer 107 in which X is  $(\text{CH}_2)_4$ .**

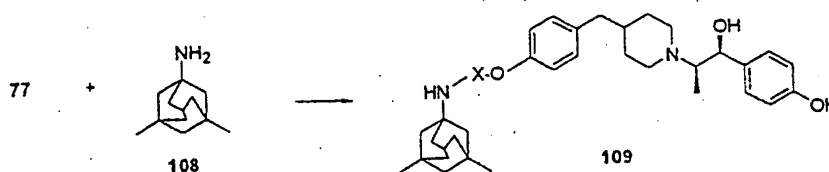


- The amine **68**, in which X is  $(\text{CH}_2)_4$  (100 mmol) is dissolved in DMF (50  
 20 mL) and the Ifenprodil oxyacetic acid, **106**, prepared as described in Preparation

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43D (100 mmol), and dicyclohexylcarbodiimide (100 mmol) are added. The progress of the reaction is monitored by tlc. When it is complete, the mixture is added to water and extracted with EtOAc. The extract is dried and evaporated, and the residue is chromatographed to afford the compound **107** in which X is  $(\text{CH}_2)_4$ .

**Example 16: Dimeric amine 109**, in which X is  $(\text{CH}_2)_4$ , incorporating the Memantidine and Eliprodil ligands.



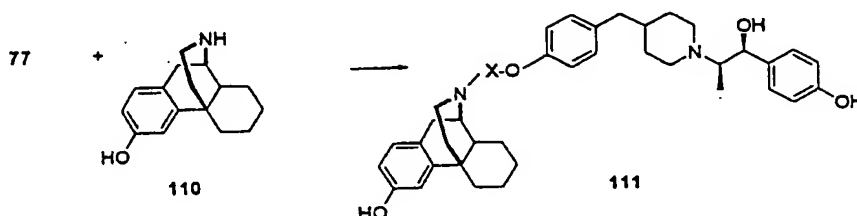
A. The bromoether **77**, in which X is  $(\text{CH}_2)_4$  (50 mmol) is dissolved in MeCN (30 mL), and memantidine (**108**) (200 mmol) and KI (25 mg) are added. The progress of the reaction is monitored by tlc. When it is complete, the mixture is added to water and extracted with  $\text{CH}_2\text{Cl}_2$ . The extract is washed with water, then dried and evaporated. The residue is dissolved in THF (50 mL) and a solution of  $\text{Bu}_4\text{NF}$  (50 mmol) in THF (50 mL) is added. After 1 hour, the solution is added to water and extracted with  $\text{CH}_2\text{Cl}_2$ . The extract is dried and evaporated, and the residue is chromatographed to afford the compound **109** in which X is  $(\text{CH}_2)_4$ .

B. Using the above procedure, the bromoethers **77** in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$  or  $(\text{CH}_2)_{18}$  are converted into the compounds **109** in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$  or  $(\text{CH}_2)_{18}$ .



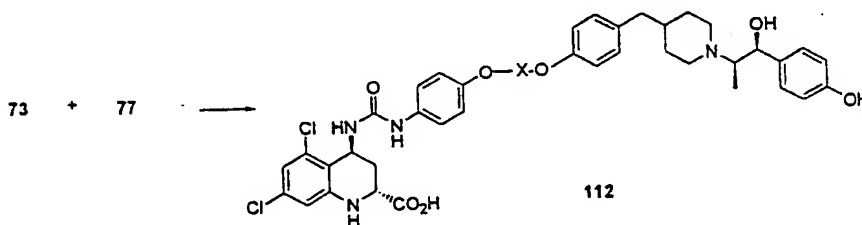
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**Example 17: Dimeric amine 111 in which X is  $(CH_2)_4$ , incorporating the Dextrorphan and Eliprodil ligands.**



- A. Using the procedure of Example 16, the bromoether 77 in which X is  $(CH_2)_4$ , is reacted with dextrorphan, 110, prepared as described in US Patent 3,810,899, to afford the tertiary amine compound 111, in which X is  $(CH_2)_4$ .
- B. Using the above procedure, the bromoethers 77 in which X is  $(CH_2CH_2O)_3CH_2CH_2$  or  $(CH_2)_{18}$  are converted into the compounds 111 in which X is  $(CH_2CH_2O)_3CH_2CH_2$  or  $(CH_2)_{18}$ .

**Example 18: Alkylation reaction to afford the ether 112, incorporating the L 689560 and Eliprodil ligands.**



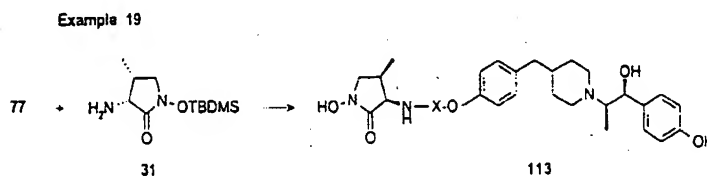
- A. The phenol 73 (50 mmol) is dissolved in MeCN (25 mL) and to the solution is added  $K_2CO_3$  (300 mg), KI (25 mg) and the bromoether 77 in which X is  $(CH_2)_4$  (50 mmol). The mixture is heated to  $60^\circ$  and the progress of the reaction is monitored by tlc. When it is complete, the solution is cooled and added to water. The aqueous solution is extracted with  $CH_2Cl_2$ . The extract is dried and evaporated, and the residue is taken up in THF. A solution of  $Bu_4NF$  (100 mmol) is added. After 1 hour, the reaction mixture is added to water and is

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extracted with  $\text{CH}_2\text{Cl}_2$ . The extract is dried and evaporated, and the residue is taken up in THF (25 mL). To the solution is added LiOH,  $\text{H}_2\text{O}$  (100 mmol), in water (25 mL). The progress of the reaction is followed by tlc. When it is complete, the reaction mixture is added to water. The pH is adjusted to 7 by addition of aqueous  $\text{NaH}_2\text{PO}_4$ , and it is then extracted with  $\text{CH}_2\text{Cl}_2$ . The extract is dried and evaporated, and the residue is chromatographed to afford the compound **112**, in which X is  $(\text{CH}_2)_4$ .

B. Using the above procedure, but employing the bromoethers 77 in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$  or  $(\text{CH}_2)_{18}$ , there are obtained the compounds 112 in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$  or  $(\text{CH}_2)_{18}$ .

**Example 19:** The dimeric ether 113, in which the ligands of Ifenprodil and HA 966 or L-687414 are connected.



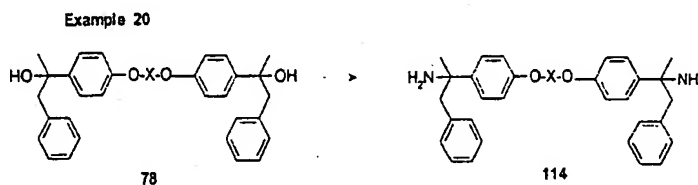
A. Using the procedure of Preparation 47, the bromoether **77** in which X is  $(\text{CH}_2)_{18}$  is reacted with the silylated amine **31** in which R is H, to afford an intermediate bis (silyl ether). This compound is treated under the conditions of Example 9B to remove the silyl protecting groups and afford the compound **113** in which X is  $(\text{CH}_2)_{18}$  and R is H.

B. Using the above procedure, but employing the amine **31** in which R is methyl, there is obtained the corresponding compound **113** in which X is  $(\text{CH}_2)_{18}$  and R is methyl.

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C. Using the above procedures, but employing the bromoethers 77 in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$  or  $(\text{CH}_2)_{18}$ , there are obtained the corresponding dimeric compounds 113 in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$  or  $(\text{CH}_2)_{18}$ .

**Example 20: Ether-linked dimer 114, in which X is  $(\text{CH}_2)_{18}$ , of the amine metabolite of Remacemide.**

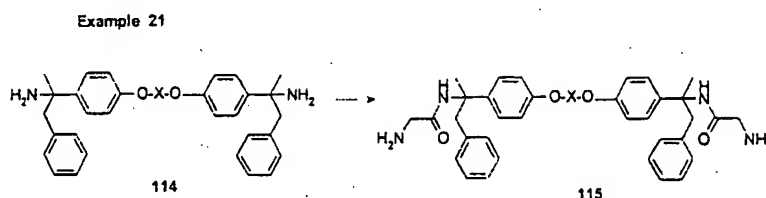


A. Using the procedure described in US Patent 5,093,524, sodium cyanide (300 mmol) is suspended in AcOH (300 mL) and n-butyl ether (60 mL) at  $0^\circ$ , and  $\text{H}_2\text{SO}_4$  (70 mL) is added in portions over a period of 20 minutes. The ice bath is removed and a solution of the bis-carbinol 78 in which X is  $(\text{CH}_2)_{18}$  (100 mmol) in n-butyl ether (50 mL) is added over a period of 2 hours. The progress of the reaction is monitored by tlc. When it is complete, the mixture is poured on to ice and extracted with  $\text{CH}_2\text{Cl}_2$ . The extract is dried and evaporated, and the residue, containing the N-formyl derivative of the final product, is suspended in 1N HCl (250 mL) and the solution is heated at reflux for 2 hours. The solution is cooled and basified with aqueous NaOH, then extracted with  $\text{CH}_2\text{Cl}_2$ . The extract is dried and evaporated, and the residue is chromatographed to afford the compound 114, in which X is  $(\text{CH}_2)_{18}$ .

B. Using the above procedure, the bis-carbinols 78, in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$  or  $(\text{CH}_2)_4$  are converted into the compounds 114 in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$  or  $(\text{CH}_2)_4$ .

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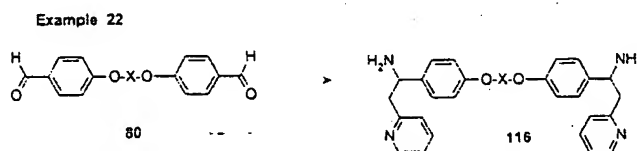
**Example 21: Remacemide ether-liked dimer 115, in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .**



A. The amine 114 in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ , prepared as described in Example 20B, (10 mmol) is dissolved in dry THF (50 mL) containing diisopropylethylamine (30 mmol) and the solution is cooled to  $-40^\circ$ . A solution of bromoacetyl chloride (25 mmol) in THF (15 mL) is added. The progress of the reaction is monitored by tlc. When it is complete, a solution of ammonia (3 g) in THF (100 mL) is added with vigorous stirring. The progress of the reaction is monitored by tlc. When it is complete, the mixture is added to water and extracted with  $\text{CH}_2\text{Cl}_2$ . The extract is dried and evaporated and the residue is chromatographed to afford the compound 115 in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .

B. Using the above procedure, the amines 114, in which X is  $(\text{CH}_2)_4$  or  $(\text{CH}_2)_{18}$ , are converted into the compounds 115 in which X is  $(\text{CH}_2)_4$  or  $(\text{CH}_2)_{18}$ .

**Example 22: Ether-linked dimer 116 of ARL 15896AR, in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .**



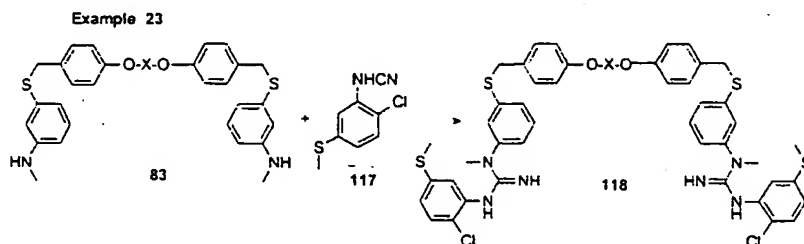
A. Using the procedure described in WO 9422831, the dialdehyde 80 in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$  (30 mmol) is dissolved in dry THF (75 mL) and the solution is cooled to  $0^\circ$ . A solution of lithium bis(trimethylsilyl) amide (60 mmol)

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in THF (50 mL) is added over 30 minutes. The mixture is maintained at 0° for 3 hours. To a separate flask containing a solution of 2-picoline (60 mmol) in THF (50 ml), at -78°, n-BuLi (60 mL of a 1M solution in hexane, 60 mmol) is added over a period of 20 minutes. This solution, containing the anion of 2-picoline, is cannulated into the first reaction mixture, and cooled to 0° over a period of 20 minutes. The cooling bath is removed and after 1 hour the mixture is added to excess dilute HCl. The aqueous solution is washed with ether, then made basic with aqueous NaOH. The basic solution is extracted with CH<sub>2</sub>Cl<sub>2</sub>. The extract is dried and evaporated to afford a residue which upon chromatography affords the amine **116**, in which X is (CH<sub>2</sub>CH<sub>2</sub>O)<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>.

B. Using the above procedure, the dialdehydes **80** in which X is (CH<sub>2</sub>)<sub>4</sub> or (CH<sub>2</sub>)<sub>18</sub> are converted into the compounds **116** in which X is (CH<sub>2</sub>)<sub>4</sub> or (CH<sub>2</sub>)<sub>18</sub>.

**Example 23: Ether-linked dimer 118, in which X is (CH<sub>2</sub>)<sub>18</sub>, of the ligand of CNS-5161.**



A. The hydrochloride of the diamine **83**, in which X is (CH<sub>2</sub>)<sub>18</sub> (10 mmol), and the cyanamide **117**, prepared as described in *J. Med. Chem.*, 1997, **40**, 4281, (12 mmol) are heated at 140-150° in chlorobenzene (10 mL) under nitrogen with stirring. The progress of the reaction is monitored by tlc. When it is complete, the solvent is removed under vacuum and the residue is chromatographed to afford the compound **118** in which X is (CH<sub>2</sub>)<sub>18</sub>.

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B. Using the above procedure, the diamines 83 in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$  or  $(\text{CH}_2)_4$  are converted into the compounds 118 in which  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$  or  $(\text{CH}_2)_4$ .

5 The above examples are illustrative only and are not meant to be indicative of the scope of the invention, which is set forth in the claims below. Those skilled in the art will recognize alternative methods and materials which may be used within the scope of the invention.

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**WHAT IS CLAIMED IS:**

1. A multibinding compound represented by Formula I:



and pharmaceutically acceptable salts thereof;

5        wherein:

each L is a ligand that may be the same or different at each occurrence;

each X is a linker that may be the same or different at each occurrence;

p is an integer of from 2 to 10; and

q is an integer of from 1 to 20;

10        wherein each of said ligands comprises a ligand domain capable of binding to a NMDA receptor, and where q is less than p.

2. The multibinding compound of claim 1, wherein each of said ligands is capable of modulating cation transport activity of the NMDA receptor.

15        3. The multibinding compound of claim 2, wherein each ligand capable of binding to an NMDA receptor is independently selected from the group consisting of glycine antagonists, glycine partial agonists, glutamate antagonists, polyamines, ion channel blockers and redox site binders.

4. The multibinding compound of claim 3, wherein at least one ligand is  
20        selected from the group consisting of L 689560, felbamate, L-701324, HA 966, L-687414, ifenprodil, eliprodil, RO-25-6981, nylidrin, SYM 2030, cycloserine, CGP-37489, CP-101606, arcaine, memantidine, dextrothorphan, detromethorphan, remacemide, ketamine, ARL 15896AR, aptiganel, MK801, CNS-5161, selfotel, flupertine, SDZ EAA 494, ketobemidone, MDL 10043, CGP-40116, NPC 12626,  
25        FR 115427, MDL 27266, licostinel, L-705022, BIII 227Cl, or derivatives thereof

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5. The multibinding compound of claim 3, wherein at least one ligand is selected from the group consisting of dexamabinol, midafotel, RO-24-6173, RO-8-4304, GPI-3000, ADCI, FPL-16283, LY-274614, WAY-126090, HO-473, CNS-1531, CP-98113, ES-2421, CNS-1044, CNS-5065, CNS-1118, CNS-1524, CNS-1505, L-701315, L-701376, L-701252, L-698532, L-687414, L-701273, LY-235959, LY-233053, LY-235723, LY-233536, EMD-95885, CGP-39653, MRZ-2/579, CP-101616, AP-6, NC-1210, PD-158473, NPS-1506 or derivatives thereof.

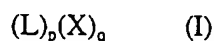
6. The multibinding compound of claim 2, wherein each divalent linker X is independently selected from a structure of Table 1.

10

7. The multibinding compound of claim 6, wherein  $p$  is an integer of from 2 to 4, and  $q$  is less than  $p$ .

8. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a therapeutically effective amount of one or more multibinding compounds represented by Formula I,

15



and pharmaceutically acceptable salts thereof;

wherein:

each L is a ligand that may be the same or different at each occurrence;

20

each X is a linker that may be the same or different at each occurrence;

$p$  is an integer of from 2 to 10; and

$q$  is an integer of from 1 to 20;

wherein each of said ligands comprises a ligand domain capable of binding to a NMDA receptor, and where  $q$  is less than  $p$ .



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9. The pharmaceutical composition of claim 8, wherein said multibinding compound or compounds is capable of modulating cation transport by the NMDA receptor to reduce pain.
10. The pharmaceutical composition of claim 9, wherein each ligand is  
 5 independently selected from the group consisting of glycine antagonists, glycine partial agonists, glutamate antagonists, polyamines, ion channel blockers and redox site binders.
11. The pharmaceutical composition of claim 10, wherein at least one ligand is selected from the group consisting of L-689560, felbamate, L-701324, HA 966, L-  
 10 687414, ifenprodil, eliprodil, RO-25-6981, nylidrin, SYM 2030, cycloserine, CGP-37489, CP-101606, arcaine, memantidine, dextrophan, detromethorphan, remacemide, ketamine, ARL 15896AR, aptiganel, MK801, CNS-5161, selfotel, flupertine, SDZ EAA 494, ketobemidone, MDL 10043, CGP-40116, NPC 12626, FR 115427, MDL 27266, licostinel, L-705022, BIII 227Cl or derivatives thereof.
12. The pharmaceutical composition of claim 9, wherein each linker X is  
 15 independently selected from a structure of Table 1.
13. The pharmaceutical composition of claim 12, wherein  $p$  is an integer of from 2 to 4, and  $q$  is less than  $p$ .
14. A method of preparing a multibinding compound represented by formula I:  

$$(L)_p(X)_q \quad (I)$$
  
 wherein each L is a ligand that may be the same or different at each occurrence;  
 X is a linker that may be the same or different at each occurrence;  
 $p$  is an integer of from 2 to 10; and  
 25  $q$  is an integer of from 1 to 20;

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wherein each of said ligands comprises a ligand domain capable of binding to a NMDA receptor, and where  $q$  is less than  $p$ ,

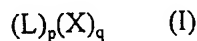
(a) providing at least  $p$  equivalents of a ligand L or precursors thereof and at least  $q$  equivalents of linker or linkers X; and

5 (b) covalently attaching said ligands to said linkers to produce a multibinding compound; or

(b') covalently attaching said ligand precursors to said linkers and completing the synthesis of said ligands thereupon, thereby to produce a multibinding compound.

10 15. The method of claim 14, wherein  $p$  is an integer of from 2 to 4, and  $q$  is less than  $p$ .

16. A method for decreasing or alleviating pain in a mammal, which method comprises administering to a mammal in need of such treatment a therapeutically effective amount of a pharmaceutical composition comprising a pharmaceutically acceptable excipient and one or more multibinding compounds represented by  
15 formula I,



and pharmaceutically acceptable salts thereof,

wherein

20 each L is a ligand that may be the same or different at each occurrence;

X is a linker that may be the same or different at each occurrence;

$p$  is an integer of from 2 to 10; and

$q$  is an integer of from 1 to 20;

wherein each of said ligands comprises a ligand domain capable of binding  
25 to a NMDA receptor, and where  $q$  is less than  $p$ .

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17. The method of claim 16, wherein  $p$  is an integer of from 2 to 4 and  $q$  is less than  $p$ .

18. A method for identifying multimeric ligand compounds possessing multibinding properties which method comprises:

- 5 (a) identifying a ligand or a mixture of ligands wherein each ligand contains at least one reactive functionality and has a ligand binding domain capable of binding to a NMDA receptor;
- (b) identifying a library of linkers wherein each linker in said library comprises at least two functional groups having complementary reactivity to at least  
10 one of the reactive functional groups of the ligand;
- (c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the ligand or mixture of ligands identified in (a) with the library of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said  
15 linker and at least two of said ligands; and
- (d) assaying the multimeric ligand compounds produced in the library prepared in (c) above to identify multimeric ligand compounds possessing multibinding properties.

19. A method for identifying multimeric ligand compounds possessing  
20 multibinding properties which method comprises:

- (a) identifying a library of ligands wherein each ligand contains at least one reactive functionality and has a ligand binding domain capable of binding to a NMDA receptor;
- (b) identifying a linker or mixture of linkers wherein each linker  
25 comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand;

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(c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the library of ligands identified in (a) with the linker or mixture of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands; and

(d) assaying the multimeric ligand compounds produced in the library prepared in (c) above to identify multimeric ligand compounds possessing multibinding properties.

20. The method according to Claim 18 or 19 wherein the preparation of the multimeric ligand compound library is achieved by either the sequential or concurrent combination of the two or more stoichiometric equivalents of the ligands identified in (a) with the linkers identified in (b).

21. The method according to Claim 20 wherein the multimeric ligand compounds comprising the multimeric ligand compound library are dimeric.

22. The method according to Claim 21 wherein the dimeric ligand compounds comprising the dimeric ligand compound library are heterodimeric.

23. The method according to Claim 22 wherein the heterodimeric ligand compound library is prepared by sequential addition of a first and second ligand.

24. The method according to Claim 18 or 19 wherein, prior to procedure (d), each member of the multimeric ligand compound library is isolated from the library.

25. The method according to Claim 24 wherein each member of the library is isolated by preparative liquid chromatography mass spectrometry (LCMS).

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26. The method according to Claim 18 or Claim 19 wherein the linker or linkers employed are selected from the group comprising flexible linkers, rigid linkers, hydrophobic linkers, hydrophilic linkers, linkers of different geometry, acidic linkers, basic linkers, linkers of different polarization and/or polarizability and amphiphilic linkers.
27. The method according to Claim 26 wherein the linkers comprise linkers of different chain length and/or having different complementary reactive groups.
28. The method according to Claim 27 wherein the linkers are selected to have different linker lengths ranging from about 2 to 100Å.
29. The method according to Claim 18 or 19 wherein the ligand or mixture of ligands is selected to have reactive functionality at different sites on said ligands.
30. The method according to Claim 29 wherein said reactive functionality is selected from the group consisting of carboxylic acids, carboxylic acid halides, carboxyl esters, amines, halides, pseudohalides, isocyanates, vinyl unsaturation, ketones, aldehydes, thiols, alcohols, anhydrides, boronates, and precursors thereof wherein the reactive functionality on the ligand is selected to be complementary to at least one of the reactive groups on the linker so that a covalent linkage can be formed between the linker and the ligand.
31. The method according to Claim 18 or Claim 19 wherein the multimeric ligand compound library comprises homomeric ligand compounds.
32. The method according to Claim 18 or Claim 19 wherein the multimeric ligand compound library comprises heteromeric ligand compounds.

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33. A library of multimeric ligand compounds which may possess multivalent properties which library is prepared by the method comprising:

(a) identifying a ligand or a mixture of ligands wherein each ligand contains at least one reactive functionality and has a ligand binding domain capable of binding to a NMDA receptor;

(b) identifying a library of linkers wherein each linker in said library comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand; and

(c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the ligand or mixture of ligands identified in (a) with the library of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands.

34. A library of multimeric ligand compounds which may possess multivalent properties which library is prepared by the method comprising:

(a) identifying a library of ligands wherein each ligand contains at least one reactive functionality and has a ligand binding domain capable of binding to a NMDA receptor;

(b) identifying a linker or mixture of linkers wherein each linker comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand; and

(c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the library of ligands identified in (a) with the linker or mixture of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands.

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35. The library according to Claim 33 or Claim 34 wherein the linker or linkers employed are selected from the group comprising flexible linkers, rigid linkers, hydrophobic linkers, hydrophilic linkers, linkers of different geometry, acidic linkers, basic linkers, linkers of different polarization and/or polarizability and  
5 amphiphilic linkers.
36. The library according to Claim 35 wherein the linkers comprise linkers of different chain length and/or having different complementary reactive groups.
37. The library according to Claim 36 wherein the linkers are selected to have different linker lengths ranging from about 2 to 100Å.
- 10 38. The library according to Claim 33 or 34 wherein the ligand or mixture of ligands is selected to have reactive functionality at different sites on said ligands.
39. The library according to Claim 38 wherein said reactive functionality is selected from the group consisting of carboxylic acids, carboxylic acid halides, carboxyl esters, amines, halides, pseudohalides, isocyanates, vinyl unsaturation,  
15 ketones, aldehydes, thiols, alcohols, anhydrides, boronates, and precursors thereof wherein the reactive functionality on the ligand is selected to be complementary to at least one of the reactive groups on the linker so that a covalent linkage can be formed between the linker and the ligand.
40. The library according to Claim 33 or Claim 34 wherein the multimeric  
20 ligand compound library comprises homomeric ligand compounds.
41. The library according to Claim 33 or Claim 34 wherein the multimeric ligand compound library comprises heteromeric ligand compounds.

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42. An iterative method for identifying multimeric ligand compounds possessing multibinding properties which method comprises:

- (a) preparing a first collection or iteration of multimeric compounds which is prepared by contacting at least two stoichiometric equivalents of the ligand or mixture of ligands which target a NMDA receptor with a linker or mixture of linkers wherein said ligand or mixture of ligands comprises at least one reactive functionality and has a ligand binding domain capable of binding to a NMDA receptor, and said linker or mixture of linkers comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand wherein said contacting is conducted under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands;
- (b) assaying said first collection or iteration of multimeric compounds to assess which if any of said multimeric compounds possess multibinding properties;
- (c) repeating the process of (a) and (b) above until at least one multimeric compound is found to possess multibinding properties;
- (d) evaluating what molecular constraints imparted or are consistent with imparting multibinding properties to the multimeric compound or compounds found in the first iteration recited in (a)- (c) above;
- (e) creating a second collection or iteration of multimeric compounds which elaborates upon the particular molecular constraints imparting multibinding properties to the multimeric compound or compounds found in said first iteration;
- (f) evaluating what molecular constraints imparted or are consistent with imparting enhanced multibinding properties to the multimeric compound or compounds found in the second collection or iteration recited in (e) above;
- (g) optionally repeating steps (e) and (f) to further elaborate upon said molecular constraints.



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43. The method according to Claim 42 wherein steps (e) and (f) are repeated from 2-50 times.

44. The method according to Claim 42 wherein steps (e) and (f) are repeated from 5-50 times.

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US99/12727

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : Please See Extra Sheet.

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/1.11, 9.1, 178.1, 193.1; 435/7.1, 7.2; 436/501, 518; 530/345, 389.1, 402, 807

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, STN (CAPLUS, BIOSIS, MEDLINE, SCISEARCH, EMBASE)

Search Terms: NMDA, multivalent, combinatorial, ligand, receptor

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y, P	GEE et al. Cyclic Peptides as Non-carboxyl-terminal Ligands of Syntrophin PDZ Domains. J. Biol. Chem. 21 August 1998, Vol. 273, No. 34, pages 21980-21987, see entire article.	1-44
Y	FERRER-MONTIEL et al. Selected Peptides Targeted to the NMDA Receptor Channel Protect Neurons from Excitotoxic Death. Nature Biotech. March 1998, Vol. 16, pages 286-291, see entire article, especially Abstract and page 286.	1-44
Y	LI, M. Use of a Modified Bacteriophage to Probe the Interactions between Peptides and Ion Channel Receptors in Mammalian Cells. Nature Biotech. June 1997, Vol. 15, pages 559-563, See entire article, especially pages 559, 560 and 562.	1-44

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*B* earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means	
*P* document published prior to the international filing date but later than the priority date claimed	

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Box PCT  
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

MAURIE E. GARCIA

Telephone No. (703) 308-0196

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US99/12727

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BERGERON et al. Impact of Polyamine Analogues on the NMDA Receptor. J. Med. Chem. 03 February 1995, Vol. 38, No. 3, pages 425-428, see entire article, especially Abstract and Scheme 2.	1-44
Y	WO 92/05802 A1 (NEORX CORPORATION) 16 April 1992 (16/04/92), see Abstract, page 3 lines 1-25, page 4 lines 20-27, page 5 lines 6-18, page 21 lines 4-33, page 22 lines 1-8 and claim 1.	1-44
Y	SHUKER et al. Discovering High-Affinity Ligands for Proteins: SAR by NMR. Science. 29 November 1996, Vol. 274, pages 1531-1534, see entire article, especially Figure 1.	18-44

INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US99/12727

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IPC (6):

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A. CLASSIFICATION OF SUBJECT MATTER:  
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- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

WO 99/64041 A1

(54) Title: MULTIBINDING AGENTS THAT MODULATE NMDA RECEPTORS

(57) Abstract: Disclosed are novel multi-binding compounds (agents) which bind to NMDA receptors. The compounds of this invention comprise a plurality of ligands each of which can bind to such receptors, thereby modulating the biological processes and/or functions thereof. Each of the ligands is covalently attached to a linker or linkers which may be the same or different to provide for the multibinding compound. The linker is selected such that the multibinding compound so constructed demonstrates increased modulation of the biological processes mediated by the NMDA receptor.

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## MULTIBINDING AGENTS THAT MODULATE NMDA RECEPTORS

### CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of United States Provisional Serial Number 60/088,466, filed June 8, 1998, and United States Provisional Serial Number 60/092,938, filed July 15, 1998.

### BACKGROUND OF THE INVENTION

#### Field of the Invention

This invention relates to novel therapeutic agents which bind to mammalian receptors and modulate their activity. More particularly, the invention relates to novel therapeutic agents that bind to and modulate the *in vivo* activity of the NMDA receptor in mammals by acting as multi-binding compounds. The therapeutic agents or multi-binding compounds described herein comprise at least two ligands connected by a linker or linkers, wherein said ligands in their monovalent state bind to and/or are capable of modulating the activity of the NMDA receptor. The linking moiety is chosen such that the multi-binding compounds so constructed demonstrate increased biological activity as compared to the same number of individual units of the ligand or ligands. The invention also relates to methods of using such compounds, to methods of preparing such compounds and to pharmaceutical compositions containing them.

These multi-binding compounds are particularly useful in treating mammalian conditions that are mediated by the NMDA receptors targeted by the ligands, such as pain sensation, Alzheimer's, cognitive disorder, dementia, schizophrenia, ocular disease, AIDS-related complex, peripheral neuropathy, CV

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ischemia, infarction, stroke, motor neuron disease, epilepsy, seizure, convulsions, neurodegenerative disease, micturation disorders, migraine, Parkinson's disease, psychosis, Huntingdon's chorea and cardiac failure. Accordingly, this invention also relates to pharmaceutical compositions comprising a pharmaceutically  
5 acceptable excipient and an effective amount of a multi-binding compound of this invention.

Publications cited herein are incorporated by reference in their entirety to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference in its entirety.

## 10 State of the Art

A receptor is a biological structure with one or more binding domains that reversibly complexes with one or more ligands, where that complexation has biological consequences.

Receptors can exist entirely outside the cell (extracellular receptors), within  
15 the cell membrane (but presenting sections of the receptor to the extracellular milieu and cytosol), or entirely within the cell (intracellular receptors). They may also function independently of a cell (e.g., clot formation). Receptors within the cell membrane allow a cell to communicate with the space outside of its boundaries (i.e., signaling) as well as to function in the transport of molecules and ions into  
20 and out of the cell.

A ligand is a binding partner for a specific receptor or family of receptors. A ligand may be the endogenous ligand for the receptor or alternatively may be a synthetic ligand for the receptor such as a drug, a drug candidate or a pharmacological tool.

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The ligands that bind to cellular receptors may be specifically classified as follows:

1. Full agonists - ligands that when bound trigger the maximum activity seen by natural ligands;
- 5        2. Partial agonists- ligands that when bound trigger sub-maximal activity;
3. Antagonist- ligands that when bound inhibit or prevent the activity arising from a natural ligand binding to the receptor. Antagonists may be of the surmountable class (results in the parallel displacement of the dose-response curve of the agonist to the right in a dose dependent fashion without reducing the
- 10       maximal response for the agonist) or insurmountable class (results in depression of the maximal response for a given agonist with or without the parallel shift);
4. Inverse antagonist-ligands that when bound decrease the basal activity of the unbound receptor (if any).

There are four fundamental measurable properties that pertain to the interaction of a ligand with its receptor:

- 1) the affinity of the ligand for the receptor, which relates to the energetics of the binding;
- 2) the efficacy of the ligand for the receptor, which relates to the functional downstream activity of the ligand;
- 20       3) the kinetics of the ligand for the receptor, which defines the onset of action and the duration of action; and
- 4) the desensitization of the receptor for the ligand.

With regard to the ligand, it is the combination of these properties that provides the foundation for defining the nature of the functional response. Thus,

25       an activating ligand (or agonist) has affinity for the receptor and downstream efficacy. In contrast, an inhibiting ligand (antagonist) has affinity for the receptor but no efficacy.



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Selectivity defines the ratios of affinities or the ratios of efficacies of a given ligand compared across two receptors. It is the selectivity of a specific drug that provides the required biological profile.

Current drugs (ligands) targeting NMDA receptors have clinical  
5 shortcomings identified by one or more of low efficacy, low affinity, poor safety profile, lack of selectivity or overselectivity for the intended receptor, and suboptimal duration of action and onset of action. Accordingly, it would be beneficial to develop ligands that have improved affinity, efficacy, selectivity, onset of action and duration of action.

10 Affinity of ligand for target receptor

An increase in ligand affinity to the target receptor may contribute to reducing the dose of ligand required to induce the desired therapeutic effect. A reduction in ligand affinity will remove activity and may contribute to the selectivity profile for a ligand.

15 Efficacy of ligand at a target receptor (functional effect)

An increased ligand efficacy at a target receptor can lead to a reduction in the dose required to mediate the desired therapeutic effect. For example, this increase in efficacy may arise from an improved positive functional response of the ligand or a change from a partial to full agonist profile. Reduced efficacy of a full  
20 agonist to a partial agonist or antagonist may provide clinical benefit by modulating the biological response.

Selectivity of ligand compared across receptor subtypes

An increase in the selectivity of the ligand across receptor subtypes requires that the affinity or efficacy of the ligand at other receptors is reduced  
25 relative to the desired receptor.

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Onset of Action

More rapid onset of action of the ligand to effect a biological response is often preferred.

Duration of Action

5       An increased duration of action of the ligand to effect a biological response may be preferred. For example  $\beta_2$  adrenergic agonists such as albuterol have a relatively short duration of action of approximately 3-4 hours and an increase in duration of action would simplify the dosing regimen required to administer this drug (ligand).

10       NMDA Receptor

      The NMDA receptor belongs to the family of ligand-gated ion channels, as described by Kemp et al., in Drugs Pharm. Sci. (1998) Vol. 89 (Receptor based Drug Design) pp. 297-321. The NMDA receptor is a ligand-gated ion channel controlled by the binding of glutamate and glycine, wherein glutamate functions as  
15       a neurotransmitter and glycine functions as a modulator, with negative allosteric interaction between glutamate and glycine binding sites. L-Glutamate is a major excitatory transmitter of the mammalian central nervous system. The NMDA receptor is also activated by the binding of N-methyl-D-aspartate, and controls the transport of calcium and sodium. It is located primarily in the brain and spinal  
20       cord.

      The NMDA receptor comprises a family of heteromers, each of which contain 5 subunits comprising an NMDAR1 subunit and four NR2 subunits which may be any of NR2<sub>A</sub>, NR2<sub>B</sub>, NR2<sub>C</sub> or NR2<sub>D</sub>. This combinatorial composition allows for subtype-specific compounds to be developed, which may affect one  
25       NMDAR1/(NR2<sub>x</sub>)<sub>4</sub> combination and not another.

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The NMDA receptor plays a key role in neurotransmission, affecting physiological functions, and neuropathological states or conditions, such as epilepsy and acute neurodegeneration. It is known that the NMDA receptor may affect many different physiological and neuropathological functions associated with various conditions, including pain sensation, Alzheimer's, cognitive disorder, dementia, schizophrenia, ocular disease, AIDS-related complex, peripheral neuropathy, CV ischemia, infarction, stroke, motor neuron disease, epilepsy, seizure, convulsions, neurodegenerative disease, micturition disorders, migraine, Parkinson's disease, psychosis, Huntingdon's chorea and cardiac failure. Other conditions may also be associated with modulation of the NMDA receptor. Thus, modulation of the NMDA receptor to achieve desired effects in each of the above conditions is desirable.

It has been found that modulation of the NMDA receptor can lead to neurotoxic and other highly undesirable side effects. For example, neurotoxic effects caused by NMDA receptor agonists appear to be associated with the high permeability to calcium, high affinity for glutamate and lack of desensitization over prolonged activation of the NMDA receptor. On the other hand, total blockade of the NMDA receptor with noncompetitive antagonists is known to cause such profound central nervous systems effects as light headedness, dizziness, paresthesia, agitation, nystagmus, hallucinations, somnolence, increase in blood pressure, catatonia and dissociative anaesthesia.

The NMDA receptor is susceptible to activity by many different potential agonists, partial agonists and antagonists due to a multiplicity of binding sites. The NMDA receptor is activated by the combined binding of both a glutamate and glycine ligand. The activation of the receptor opens the cation channel, creating a potential binding site for an ion channel blocker. Further, it has been shown that The NMDA receptor can receive polyamine ligands, has a zinc binding site and a

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magnesium binding site, is subject to phosphorylation and has a redox site. Activation or modulation of any of the sites affects various changes in the activity of the NMDA receptor.

Accordingly, novel ligands having desired potency for and therapeutic effects at the NMDA receptor would be particularly desirable in order to modulate the cation transport activity of the NMDA receptor, especially in the case of pain in mammalian patients. Such novel ligands would preferably achieve the desired potency and therapeutic effect by modulating one or more of the ligand's properties as to efficacy, affinity, safety profile, selectivity, duration of action and/or onset of action. This may have advantages in the effects on other disease states as well, such as Alzheimer's, cognitive disorder, dementia, schizophrenia, ocular disease, AIDS-related complex, peripheral neuropathy, CV ischemia, infarction, stroke, motor neuron disease, epilepsy, seizure, convulsions, neurodegenerative disease, micturition disorders, migraine, Parkinson's disease, psychosis, Huntingdon's chorea and cardiac failure.

### SUMMARY OF THE INVENTION

This invention is directed to general synthetic methods for generating large libraries of diverse multimeric compounds which multimeric compounds are candidates for possessing multibinding properties. The diverse multimeric compound libraries provided by this invention are synthesized by combining a linker or linkers with a ligand or ligands to provide for a library of multimeric compounds wherein the linker and ligand each have complementary functional groups permitting covalent linkage. The library of linkers is preferably selected to have diverse properties such as valency, linker length, linker geometry and rigidity, hydrophilicity or hydrophobicity, amphiphilicity, acidity, basicity and polarization. The library of ligands is preferably selected to have diverse

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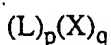
attachment points on the same ligand, different functional groups at the same site of otherwise the same ligand, and the like.

This invention is also directed to libraries of diverse multimeric compounds which multimeric compounds are candidates for possessing multibinding properties. These libraries are prepared via the methods described above and permit the rapid and efficient evaluation of what molecular constraints impart multibinding properties to a ligand or a class of ligands targeting a receptor.

Accordingly, in one of its compositional aspects, this invention is directed to multi-binding compounds and salts thereof comprising 2 to 10 ligands, which may be the same or different and which are covalently attached to a linker or linkers which may be the same or different, at least one of said ligands comprising a ligand domain capable of binding to a NMDA receptor.

The multi-binding compounds of this invention are preferably represented by formula I:

15



I

wherein each L is independently selected from ligands comprising a ligand domain capable of binding to a NMDA receptor; X is independently a linker;  $p$  is an integer of from 2 to 10;  $q$  is an integer of from 1 to 20; and pharmaceutically acceptable salts thereof. Preferably,  $q$  is less than  $p$ .

20

In another of its composition aspects, this invention is directed to a pharmaceutical composition comprising a pharmaceutically acceptable excipient and an effective amount of a multi-binding compound, or a pharmaceutically acceptable salt thereof, comprising 2 to 10 ligands which may be the same or different and which are covalently attached to a linker or linkers which may be the

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same or different, at least one of said ligands comprising a ligand domain capable of binding to a NMDA receptor.

Preferably, said ligands comprising a ligand domain capable of binding to a NMDA receptor modulate cation transport, particularly calcium and sodium transport, in mammals. More preferably, said ligands are selected from the group consisting of L-689560, felbamate, L-701324, HA 966, L-687414, ifenprodil, eliprodil, RO-25-6981, nylidrin, SYM 2030, cycloserine, CGP-37489, CP-101606, arcaine, memantidine, dextrorphan, detromethorphan, remacemide, ketamine, ARL 15896AR, aptiganel, MK801, CNS-5161, selfotel, flupertine, SDZ EAA 494, ketobemidone, MDL 10043, CGP-40116, NPC 12626, FR 115427, MDL 27266, licostinel, L-705022, and BIII 227Cl, and derivatives thereof. In all embodiments, at least one ligand has a ligand binding domain capable of binding to a NMDA receptor.

In still another of its composition aspects, this invention is directed to a pharmaceutical composition comprising a pharmaceutically acceptable excipient and an effective amount of a multi-binding compound represented by formula I:



wherein each L is independently selected from ligands comprising a ligand domain capable of binding to a NMDA receptor; X is a linker;  $p$  is an integer of from 2 to 10;  $q$  is an integer of from 1 to 20; and pharmaceutically acceptable salts thereof. Preferably,  $q$  is less than  $p$ , and more preferably the ligand is selected from the group consisting of L-689560, felbamate, L-701324, HA 966, L-687414, ifenprodil, eliprodil, RO-25-6981, nylidrin, SYM 2030, cycloserine, CGP-37489, CP-101606, arcaine, memantidine, dextrorphan, detromethorphan, remacemide, ketamine, ARL 15896AR, aptiganel, MK801, CNS-5161, selfotel, flupertine, SDZ

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EAA 494, ketobemidone, MDL 10043, CGP-40116, NPC 12626, FR 115427, MDL 27266, licostinel, L-705022, and BIII 227C1, and derivatives thereof.

In one of its method aspects, this invention is directed to a method for modulating cation transport by a NMDA receptor in a mammal, which method comprises administering to said mammal an effective amount of a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a multi-binding compound, or a pharmaceutically acceptable salt thereof, comprising 2 to 10 ligands which may be the same or different and which are covalently attached to a linker or linkers which may be the same or different, at least two of said ligands comprising a ligand domain capable of binding to a NMDA receptor.

In another of its method aspects, this invention is directed to a method for treating diseases or conditions including pain sensation, Alzheimer's, cognitive disorder, dementia, schizophrenia, ocular disease, AIDS-related complex, peripheral neuropathy, CV ischemia, infarction, stroke, motor neuron disease, epilepsy, seizure, convulsions, neurodegenerative disease, micturition disorders, migraine, Parkinson's disease, psychosis, Huntingdon's chorea and cardiac failure, particularly pain sensation, in a mammal mediated by NMDA receptors which method comprises administering to said mammal an effective amount of a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a multi-binding compound represented by formula I:



wherein each L is independently selected from ligands comprising a ligand domain capable of binding to a NMDA receptor mediating cation transport; X is a linker;  $p$  is an integer of from 2 to 10;  $q$  is an integer of from 1 to 20 and pharmaceutically acceptable salts thereof.

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Preferably,  $q$  is less than  $p$ , and more preferably, the ligand is selected from the group consisting of ligands having a ligand binding domain capable of binding to a NMDA receptor as set forth in detail herein.

Accordingly, in one of its method aspects, this invention is directed to a method for identifying multimeric ligand compounds possessing multibinding properties which method comprises:

- (a) identifying a ligand or a mixture of ligands wherein each ligand contains at least one reactive functionality;
- (b) identifying a library of linkers wherein each linker in said library comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand;
- (c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the ligand or mixture of ligands identified in (a) with the library of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands; and
- (d) assaying the multimeric ligand compounds produced in (c) above to identify multimeric ligand compounds possessing multibinding properties.

In another of its method aspects, this invention is directed to a method for identifying multimeric ligand compounds possessing multibinding properties which method comprises:

- (a) identifying a library of ligands wherein each ligand contains at least one reactive functionality;
- (b) identifying a linker or mixture of linkers wherein each linker comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand;



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- (c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the library of ligands identified in (a) with the linker or mixture of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands; and
- (d) assaying the multimeric ligand compounds produced in (c) above to identify multimeric ligand compounds possessing multibinding properties.

The preparation of the multimeric ligand compound library is achieved by either the sequential or concurrent combination of the two or more stoichiometric equivalents of the ligands identified in (a) with the linkers identified in (b). Sequential addition is preferred when a mixture of different ligands is employed to ensure heterodimeric or multimeric compounds are prepared. Concurrent addition of the ligands is preferred when at least a portion of the multimeric compounds prepared are homomultimeric compounds.

The assay protocols recited in (d) can be conducted on the multimeric ligand compound library produced in (c) above, or preferably, each member of the library is isolated by preparative liquid chromatography mass spectrometry (LCMS).

In one of its composition aspects, this invention is directed to a library of multimeric ligand compounds which may possess multivalent properties which library is prepared by the method comprising:

- (a) identifying a ligand or a mixture of ligands wherein each ligand contains at least one reactive functionality;
- (b) identifying a library of linkers wherein each linker in said library comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand; and

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- (c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the ligand or mixture of ligands identified in (a) with the library of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands.

In another of its composition aspects, this invention is directed to a library of multimeric ligand compounds which may possess multivalent properties which library is prepared by the method comprising:

- (a) identifying a library of ligands wherein each ligand contains at least one reactive functionality;
- (b) identifying a linker or mixture of linkers wherein each linker comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand; and
- (c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the library of ligands identified in (a) with the linker or mixture of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands.

In a preferred embodiment, the library of linkers employed in either the methods or the library aspects of this invention is selected from the group comprising flexible linkers, rigid linkers, hydrophobic linkers, hydrophilic linkers, linkers of different geometry, acidic linkers, basic linkers, linkers of different polarization and/or polarizability and amphiphilic linkers. For example, in one embodiment, each of the linkers in the linker library may comprise linkers of different chain length and/or having different complementary reactive groups. Such linker lengths can preferably range from about 2 to 100Å.

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In another preferred embodiment, the ligand or mixture of ligands is selected to have reactive functionality at different sites on said ligands in order to provide for a range of orientations of said ligand on said multimeric ligand compounds. Such reactive functionality includes, by way of example, carboxylic acids, carboxylic acid halides, carboxyl esters, amines, halides, pseudohalides, isocyanates, vinyl unsaturation, ketones, aldehydes, thiols, alcohols, anhydrides, boronates and precursors thereof. It is understood, of course, that the reactive functionality on the ligand is selected to be complementary to at least one of the reactive groups on the linker so that a covalent linkage can be formed between the linker and the ligand.

In other embodiments, the multimeric ligand compound is homomeric (i.e., each of the ligands is the same ligand having a ligand binding domain capable of binding to a NMDA receptor, although it may be attached at different points) or heteromeric (i.e., at least one of the ligands is different from the other ligands).

In addition to the combinatorial methods described herein, this invention provides for an iterative process for rationally evaluating what molecular constraints impart multibinding properties to a class of multimeric compounds or ligands targeting a receptor. Specifically, this method aspect is directed to a method for identifying multimeric ligand compounds possessing multibinding properties which method comprises:

(a) preparing a first collection or iteration of multimeric compounds which is prepared by contacting at least two stoichiometric equivalents of the ligand or mixture of ligands which target a receptor with a linker or mixture of linkers wherein said ligand or mixture of ligands comprises at least one reactive functionality and said linker or mixture of linkers comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand wherein said contacting is conducted under conditions

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wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands;

- (b) assaying said first collection or iteration of multimeric compounds to assess which if any of said multimeric compounds possess multibinding properties;
- (c) repeating the process of (a) and (b) above until at least one multimeric compound is found to possess multibinding properties;
- (d) evaluating what molecular constraints imparted multibinding properties to the multimeric compound or compounds found in the first iteration recited in (a)- (c) above;
- (e) creating a second collection or iteration of multimeric compounds which elaborates upon the particular molecular constraints imparting multibinding properties to the multimeric compound or compounds found in said first iteration;
- (f) evaluating what molecular constraints imparted enhanced multibinding properties to the multimeric compound or compounds found in the second collection or iteration recited in (e) above;
- (g) optionally repeating steps (e) and (f) to further elaborate upon said molecular constraints.

Preferably, steps (e) and (f) are repeated at least two times, more preferably at least from 2-50 times, even more preferably from at least 3 to 50 times, and still more preferably at least 5-50 times.

### DETAILED DESCRIPTION OF THE INVENTION

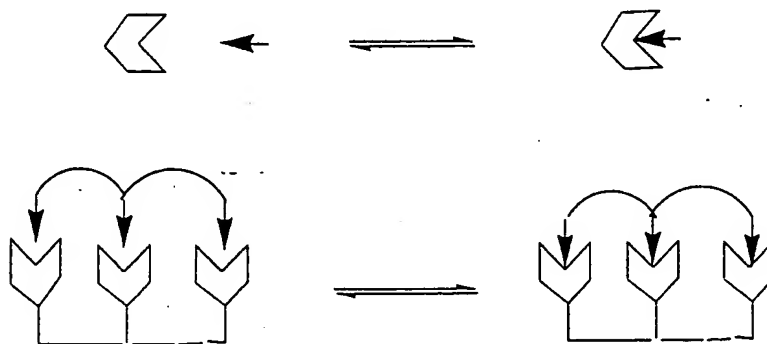
Ligand (drug) interactions with cellular receptors are controlled by molecular interaction/recognition between the ligand and the receptor. In turn, such interaction can result in modulation or disruption of the biological processes/functions of these receptors and, in some cases, leads to cell death. Accordingly, when cellular receptors mediate mammalian pathologic conditions,

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interactions of the ligand with the cellular receptor can be used to treat these conditions. Of particular interest are mammalian NMDA receptors which are known to affect cation transport, especially calcium and sodium transport, as well as other important functions. As noted above, this invention is directed, in part, to multi-binding compounds that bind NMDA receptors.

The "affinity" and "specificity" of the NMDA receptors and ligands thereto are dependent upon the complementarity of molecular binding surfaces and the energetic costs of complexation. "Affinity" is sometimes quantified by the equilibrium constant of complex formation. Specificity relates to the difference in affinity between the same ligand binding to different ligand binding sites on the cellular receptor.

The multi-binding compounds of this invention are capable of acting as multi-binding agents and the surprising activity of these compounds arises at least in part from their ability to bind in a multivalent manner with mammalian NMDA receptors. Multivalent binding interactions are characterized by the concurrent interaction of multiple ligands with multiple ligand binding sites on NMDA receptors. Multivalent interactions differ from collections of individual monovalent interactions by imparting enhanced biological and/or therapeutic effect. Examples of multivalent binding interaction (e.g., trivalent) relative to a monovalent binding interaction is shown below:



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Just as multivalent binding can amplify binding affinities, it can also amplify differences in binding affinities, resulting in enhanced binding specificity as well as affinity.

Definitions:

5 Prior to discussing this invention in further detail, the following terms will first be defined.

The term "alkyl" refers to a monoradical branched or unbranched saturated hydrocarbon chain preferably having from 1 to 40 carbon atoms, more preferably 1 to 10 carbon atoms, and even more preferably 1 to 6 carbon atoms. This term is  
10 exemplified by groups such as methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *n*-hexyl, *n*-decyl, tetradecyl, and the like.

The term "substituted alkyl" refers to an alkyl group as defined above, having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted  
15 cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocycloxy, thiol, thioalkoxy, substituted thioalkoxy,  
aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocycloxy, hydroxy-  
20 amino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO<sub>2</sub>-alkyl, -SO<sub>2</sub>-substituted alkyl, -SO<sub>2</sub>-aryl and -SO<sub>2</sub>-heteroaryl.

The term "alkylene" refers to a diradical of a branched or unbranched saturated hydrocarbon chain, preferably having from 1 to 40 carbon atoms, more preferably 1 to 10 carbon atoms and even more preferably 1 to 6 carbon atoms.  
25 This term is exemplified by groups such as methylene (-CH<sub>2</sub>-), ethylene

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(-CH<sub>2</sub>CH<sub>2</sub>-), the propylene isomers (e.g., -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>- and -CH(CH<sub>3</sub>)CH<sub>2</sub>-) and the like.

The term "substituted alkylene" refers to an alkylene group, as defined above, having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO<sub>2</sub>-alkyl, -SO<sub>2</sub>-substituted alkyl, -SO<sub>2</sub>-aryl and -SO<sub>2</sub>-heteroaryl. Additionally, such substituted alkylene groups include those where 2 substituents on the alkylene group are fused to form one or more cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heterocyclic or heteroaryl groups fused to the alkylene group. Preferably such fused groups contain from 1 to 3 fused ring structures.

The term "alkaryl" refers to the groups -alkylene-aryl and -substituted alkylene-aryl where alkylene, substituted alkylene and aryl are defined herein. Such alkaryl groups are exemplified by benzyl, phenethyl and the like.

The term "alkoxy" refers to the groups alkyl-O-, alkenyl-O-, cycloalkyl-O-, cycloalkenyl-O-, and alkynyl-O-, where alkyl, alkenyl, cycloalkyl, cycloalkenyl, and alkynyl are as defined herein. Preferred alkoxy groups are alkyl-O- and include, by way of example, methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *tert*-butoxy, *sec*-butoxy, *n*-pentoxy, *n*-hexoxy, 1,2-dimethylbutoxy, and the like.

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The term "substituted alkoxy" refers to the groups substituted alkyl-O-, substituted alkenyl-O-, substituted cycloalkyl-O-, substituted cycloalkenyl-O-, and substituted alkynyl-O- where substituted alkyl, substituted alkenyl, substituted cycloalkyl, substituted cycloalkenyl and substituted alkynyl are as defined herein.

5       The term "alkylalkoxy" refers to the groups -alkylene-O-alkyl, -alkylene-O-substituted alkyl, -substituted alkylene-O-alkyl and -substituted alkylene-O-substituted alkyl wherein alkyl, substituted alkyl, alkylene and substituted alkylene are as defined herein. Preferred alkylalkoxy groups are alkylene-O-alkyl and include, by way of example, methylenemethoxy  
10       (-CH<sub>2</sub>OCH<sub>3</sub>), ethylenemethoxy (-CH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>), *n*-propylene-*iso*-propoxy (-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>OCH(CH<sub>3</sub>)<sub>2</sub>), methylene-*t*-butoxy (-CH<sub>2</sub>-O-C(CH<sub>3</sub>)<sub>3</sub>) and the like.

The term "alkylthioalkoxy" refers to the group -alkylene-S-alkyl, alkylene-S-substituted alkyl, substituted alkylene-S-alkyl and substituted alkylene-S-substituted alkyl wherein alkyl, substituted alkyl, alkylene and substituted  
15       alkylene are as defined herein. Preferred alkylthioalkoxy groups are alkylene-S-alkyl and include, by way of example, methylenethiomethoxy (-CH<sub>2</sub>SCH<sub>3</sub>), ethylenethiomethoxy (-CH<sub>2</sub>CH<sub>2</sub>SCH<sub>3</sub>), *n*-propylene-*iso*-thiopropoxy (-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SCH(CH<sub>3</sub>)<sub>2</sub>), methylene-*t*-thiobutoxy (-CH<sub>2</sub>SC(CH<sub>3</sub>)<sub>3</sub>) and the like.

20       The term "alkenyl" refers to a monoradical of a branched or unbranched unsaturated hydrocarbon group preferably having from 2 to 40 carbon atoms, more preferably 2 to 10 carbon atoms and even more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-6 sites of vinyl unsaturation. Preferred  
25       alkenyl groups include ethenyl (-CH=CH<sub>2</sub>), *n*-propenyl (-CH<sub>2</sub>CH=CH<sub>2</sub>), *iso*-propenyl (-C(CH<sub>3</sub>)=CH<sub>2</sub>), and the like.



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The term "substituted alkenyl" refers to an alkenyl group as defined above having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocycloxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocycloxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO<sub>2</sub>-alkyl, -SO<sub>2</sub>-substituted alkyl, -SO<sub>2</sub>-aryl and -SO<sub>2</sub>-heteroaryl.

The term "alkenylene" refers to a diradical of a branched or unbranched unsaturated hydrocarbon group preferably having from 2 to 40 carbon atoms, more preferably 2 to 10 carbon atoms and even more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-6 sites of vinyl unsaturation. This term is exemplified by groups such as ethenylene (-CH=CH-), the propenylene isomers (e.g., -CH<sub>2</sub>CH=CH- and -C(CH<sub>3</sub>)=CH-) and the like.

The term "substituted alkenylene" refers to an alkenylene group as defined above having from 1 to 5 substituents, and preferably from 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocycloxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocycloxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO<sub>2</sub>-alkyl, -SO<sub>2</sub>-substituted alkyl, -SO<sub>2</sub>-aryl and -SO<sub>2</sub>-heteroaryl.

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Additionally, such substituted alkenylene groups include those where 2 substituents on the alkenylene group are fused to form one or more cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heterocyclic or heteroaryl groups fused to the alkenylene group.

5           The term "alkynyl" refers to a monoradical of an unsaturated hydrocarbon preferably having from 2 to 40 carbon atoms, more preferably 2 to 20 carbon atoms and even more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-6 sites of acetylene (triple bond) unsaturation. Preferred alkynyl groups include ethynyl ( $-C\equiv CH_2$ ), propargyl ( $-CH_2C\equiv CH$ ) and the like.

10           The term "substituted alkynyl" refers to an alkynyl group as defined above having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, 15 halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocycloxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocycloxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO<sub>2</sub>-alkyl, -SO<sub>2</sub>-substituted alkyl, -SO<sub>2</sub>-aryl and -SO<sub>2</sub>-heteroaryl.

20           The term "alkynylene" refers to a diradical of an unsaturated hydrocarbon preferably having from 2 to 40 carbon atoms, more preferably 2 to 10 carbon atoms and even more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-6 sites of acetylene (triple bond) unsaturation. Preferred alkynylene groups include ethynylene ( $-C\equiv C-$ ), propargylene ( $-CHC\equiv C-$ ) and the 25 like.

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The term "substituted alkynylene" refers to an alkynylene group as defined above having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocycloxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocycloxy, hydroxy-amino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO<sub>2</sub>-alkyl, -SO<sub>2</sub>-substituted alkyl, -SO<sub>2</sub>-aryl and -SO<sub>2</sub>-heteroaryl.

The term "acyl" refers to the groups HC(O)-, alkyl-C(O)-, substituted alkyl-C(O)-, cycloalkyl-C(O)-, substituted cycloalkyl-C(O)-, cycloalkenyl-C(O)-, substituted cycloalkenyl-C(O)-, aryl-C(O)-, heteroaryl-C(O)- and heterocyclic-C(O)- where alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic are as defined herein.

The term "acylamino" refers to the group -C(O)NRR where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, heterocyclic or where both R groups are joined to form a heterocyclic group (e.g., morpholino) wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

The term "aminoacyl" refers to the group -NRC(O)R where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

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The term "aminoacyloxy" refers to the group -NRC(O)OR where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

5       The term "acyloxy" refers to the groups alkyl-C(O)O-, substituted alkyl-C(O)O-, cycloalkyl-C(O)O-, substituted cycloalkyl-C(O)O-, aryl-C(O)O-, heteroaryl-C(O)O-, and heterocyclic-C(O)O- wherein alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl, and heterocyclic are as defined herein.

10       The term "aryl" refers to an unsaturated aromatic carbocyclic group of from 6 to 20 carbon atoms having a single ring (e.g., phenyl) or multiple condensed (fused) rings (e.g., naphthyl or anthryl). Preferred aryls include phenyl, naphthyl and the like.

15       Unless otherwise constrained by the definition for the aryl substituent, such aryl groups can optionally be substituted with from 1 to 5 substituents, preferably 1 to 3 substituents, selected from the group consisting of acyloxy, hydroxy, thiol, acyl, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkoxy, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted cycloalkenyl, amino, substituted amino, aminoacyl, acylamino, alkaryl, 20   aryl, aryloxy, azido, carboxyl, carboxylalkyl, cyano, halo, nitro, heteroaryl, heteroaryloxy, heterocyclic, heterocycloxy, aminoacyloxy, oxyacylamino, thioalkoxy, substituted thioalkoxy, thioaryloxy, thioheteroaryloxy, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO<sub>2</sub>-alkyl, -SO<sub>2</sub>-substituted alkyl, -SO<sub>2</sub>-aryl, -SO<sub>2</sub>-heteroaryl and trihalomethyl. Preferred aryl substituents include 25   alkyl, alkoxy, halo, cyano, nitro, trihalomethyl, and thioalkoxy.

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The term "aryloxy" refers to the group aryl-O- wherein the aryl group is as defined above including optionally substituted aryl groups as also defined above.

The term "arylene" refers to the diradical derived from aryl (including substituted aryl) as defined above and is exemplified by 1,2-phenylene, 1,3-phenylene, 1,4-phenylene, 1,2-naphthylene and the like.

The term "amino" refers to the group  $\text{-NH}_2$ .

The term "substituted amino" refers to the group -NRR where each R is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl and heterocyclic provided that both R's are not hydrogen.

The term "carboxyalkyl" refers to the groups "-C(O)O-alkyl", "-C(O)O-substituted alkyl", "-C(O)O-cycloalkyl", "-C(O)O-substituted cycloalkyl", "-C(O)O-alkenyl", "-C(O)O-substituted alkenyl", "-C(O)O-alkynyl" and "-C(O)O-substituted alkynyl" where alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl and substituted alkynyl are as defined herein.

The term "cycloalkyl" refers to cyclic alkyl groups of from 3 to 20 carbon atoms having a single cyclic ring or multiple condensed rings. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclooctyl, and the like, or multiple ring structures such as adamantanyl, and the like.

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The term "substituted cycloalkyl" refers to cycloalkyl groups having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO<sub>2</sub>-alkyl, -SO<sub>2</sub>-substituted alkyl, -SO<sub>2</sub>-aryl and -SO<sub>2</sub>-heteroaryl.

The term "cycloalkenyl" refers to cyclic alkenyl groups of from 4 to 20 carbon atoms having a single cyclic ring and at least one point of internal unsaturation. Examples of suitable cycloalkenyl groups include, for instance, cyclobut-2-enyl, cyclopent-3-enyl, cyclooct-3-enyl and the like.

The term "substituted cycloalkenyl" refers to cycloalkenyl groups having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO<sub>2</sub>-alkyl, -SO<sub>2</sub>-substituted alkyl, -SO<sub>2</sub>-aryl and -SO<sub>2</sub>-heteroaryl.

The term "halo" or "halogen" refers to fluoro, chloro, bromo and iodo.

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The term "heteroaryl" refers to an aromatic group of from 1 to 15 carbon atoms and 1 to 4 heteroatoms selected from oxygen, nitrogen and sulfur within at least one ring (if there is more than one ring).

Unless otherwise constrained by the definition for the heteroaryl

5 substituent, such heteroaryl groups can be optionally substituted with 1 to 5 substituents, preferably 1 to 3 substituents, selected from the group consisting of acyloxy, hydroxy, thiol, acyl, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkoxy, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted cycloalkenyl, amino, substituted amino,

10 aminoacyl, acylamino, alkaryl, aryl, aryloxy, azido, carboxyl, carboxylalkyl, cyano, halo, nitro, heteroaryl, heteroaryloxy, heterocyclic, heterocycloxy, aminoacyloxy, oxyacylamino, thioalkoxy, substituted thioalkoxy, thioaryloxy, thioheteroaryloxy, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO<sub>2</sub>-alkyl, -SO<sub>2</sub>-substituted alkyl, -SO<sub>2</sub>-aryl, -SO<sub>2</sub>-heteroaryl and trihalomethyl.

15 Preferred aryl substituents include alkyl, alkoxy, halo, cyano, nitro, trihalomethyl, and thioalkoxy. Such heteroaryl groups can have a single ring (e.g., pyridyl or furyl) or multiple condensed rings (e.g., indolizinyl or benzothienyl). Preferred heteroaryls include pyridyl, pyrrolyl and furyl.

The term "heteroaryloxy" refers to the group heteroaryl-O-.

20 The term "heteroarylene" refers to the diradical group derived from heteroaryl (including substituted heteroaryl), as defined above, and is exemplified by the groups 2,6-pyridylene, 2,4-pyridylene, 1,2-quinolinyne, 1,8-quinolinyne, 1,4-benzofuranylene, 2,5-pyridnylene, 2,5-indolenyl and the like.

The term "heterocycle" or "heterocyclic" refers to a monoradical saturated

25 unsaturated group having a single ring or multiple condensed rings, from 1 to 40

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carbon atoms and from 1 to 10 hetero atoms, preferably 1 to 4 heteroatoms, selected from nitrogen, sulfur, phosphorus, and/or oxygen within the ring.

Unless otherwise constrained by the definition for the heterocyclic substituent, such heterocyclic groups can be optionally substituted with 1 to 5, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocycloxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocycloxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO<sub>2</sub>-alkyl, -SO<sub>2</sub>-substituted alkyl, -SO<sub>2</sub>-aryl and -SO<sub>2</sub>-heteroaryl. Such heterocyclic groups can have a single ring or multiple condensed rings. Preferred heterocyclics include morpholino, piperidiny, and the like.

Examples of nitrogen heterocycles and heteroaryls include, but are not limited to, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthylpyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole, phenoxazine, phenothiazine, imidazolidine, imidazoline, piperidine, piperazine, indoline, morpholino, piperidiny, tetrahydrofuranyl, and the like as well as N-alkoxy-nitrogen containing heterocycles.

A preferred class of heterocyclics include "crown compounds" which refers to a specific class of heterocyclic compounds having one or more repeating



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units of the formula  $[-(\text{CH}_2)_m\text{Y}]$  where  $m$  is  $\geq 2$ , and Y at each separate occurrence can be O, N, S or P. Examples of crown compounds include, by way of example only,  $[-(\text{CH}_2)_3\text{NH}]_3$ ,  $[-((\text{CH}_2)_2\text{O})_4-((\text{CH}_2)_2\text{NH})_2]$  and the like. Typically such crown compounds can have from 4 to 10 heteroatoms and 8 to 40 carbon atoms.

The term "heterocyclooxy" refers to the group heterocyclic-O-.

The term "thioheterocyclooxy" refers to the group heterocyclic-S-.

The term "heterocyclene" refers to the diradical group formed from a heterocycle, as defined herein, and is exemplified by the groups 2,6-morpholino, 2,5-morpholino and the like.

The term "oxyacylamino" refers to the group  $-\text{OC}(\text{O})\text{NRR}$  where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

The term "pseudohalide" refers to functional groups which react in displacement reactions in a manner similar to a halogen. Such functional groups include, by way of example, mesyl, tosyl, azido and cyano groups.

The term "thiol" refers to the group -SH.

The term "thioalkoxy" refers to the group -S-alkyl.

The term "substituted thioalkoxy" refers to the group -S-substituted alkyl.

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The term "thioaryloxy" refers to the group aryl-S- wherein the aryl group is as defined above including optionally substituted aryl groups also defined above.

5 The term "thioheteroaryloxy" refers to the group heteroaryl-S- wherein the heteroaryl group is as defined above including optionally substituted aryl groups as also defined above.

As to any of the above groups which contain one or more substituents, it is understood, of course, that such groups do not contain any substitution or substitution patterns which are sterically impractical and/or synthetically non-feasible. In addition, the compounds of this invention include all stereochemical  
10 isomers arising from the substitution of these compounds.

The term "pharmaceutically acceptable salt" refers to salts which retain the biological effectiveness and properties of the multi-binding compounds of this invention and which are not biologically or otherwise undesirable. In many cases, the multi-binding compounds of this invention are capable of forming acid and/or  
15 base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto.

Pharmaceutically acceptable base addition salts can be prepared from inorganic and organic bases. Salts derived from inorganic bases, include by way of example only, sodium, potassium, lithium, ammonium, calcium and magnesium  
20 salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary and tertiary amines, such as alkyl amines, dialkyl amines, trialkyl amines, substituted alkyl amines, di(substituted alkyl) amines, tri(substituted alkyl) amines, alkenyl amines, dialkenyl amines, trialkenyl amines, substituted alkenyl amines, di(substituted alkenyl) amines, tri(substituted alkenyl)  
25 amines, cycloalkyl amines, di(cycloalkyl) amines, tri(cycloalkyl) amines,

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substituted cycloalkyl amines, disubstituted cycloalkyl amine, trisubstituted cycloalkyl amines, cycloalkenyl amines, di(cycloalkenyl) amines, tri(cycloalkenyl) amines, substituted cycloalkenyl amines, disubstituted cycloalkenyl amine, trisubstituted cycloalkenyl amines, aryl amines, diaryl amines, triaryl amines, heteroaryl amines, diheteroaryl amines, triheteroaryl amines, heterocyclic amines, diheterocyclic amines, triheterocyclic amines, mixed di- and tri-amines where at least two of the substituents on the amine are different and are selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic, and the like. Also included are amines where the two or three substituents, together with the amino nitrogen, form a heterocyclic or heteroaryl group.

Examples of suitable amines include, by way of example only, isopropylamine, trimethyl amine, diethyl amine, tri(*iso*-propyl) amine, tri(*n*-propyl) amine, ethanolamine, 2-dimethylaminoethanol, tromethamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, N-alkylglucamines, theobromine, purines, piperazine, piperidine, morpholine, N-ethylpiperidine, and the like. It should also be understood that other carboxylic acid derivatives would be useful in the practice of this invention, for example, carboxylic acid amides, including carboxamides, lower alkyl carboxamides, dialkyl carboxamides, and the like.

Pharmaceutically acceptable acid addition salts may be prepared from inorganic and organic acids. Salts derived from inorganic acids include hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Salts derived from organic acids include acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid,

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mandelic acid, methanesulfonic acid, ethanesulfonic acid, *p*-toluene-sulfonic acid, salicylic acid, and the like.

5       The term "protecting group" or "blocking group" refers to any group which when bound to one or more hydroxyl, thiol, amino or carboxyl groups of the compounds (including intermediates thereof) prevents reactions from occurring at these groups and which protecting group can be removed by conventional chemical or enzymatic steps to reestablish the hydroxyl, thiol, amino or carboxyl group (Green, *Protective Groups in Organic Synthesis*, 2<sup>nd</sup> Ed., John Wiley & Sons, NY, NY (1991)). The particular removable blocking group employed is not  
10       critical and preferred removable hydroxyl blocking groups include conventional substituents such as allyl, benzyl, acetyl, chloroacetyl, thiobenzyl, benzylidene, phenacyl, *t*-butyl-diphenylsilyl and any other group that can be introduced chemically onto a hydroxyl functionality and later selectively removed either by chemical or enzymatic methods in mild conditions compatible with the nature of  
15       the product.

Preferred removable amino blocking groups include conventional substituents such as *t*-butoxycarbonyl (*t*-BOC), benzyloxycarbonyl (CBZ), and the like which can be removed by conventional conditions compatible with the nature of the product.

20       Preferred carboxyl protecting groups include esters such as methyl, ethyl, propyl, *t*-butyl etc. which can be removed by mild hydrolysis conditions compatible with the nature of the product.

The term "optional" or "optionally" means that the subsequently described event, circumstance or substituent may or may not occur, and that the description

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includes instances where said event or circumstance occurs and instances where it does not.

As used herein, the terms "inert organic solvent" or "inert solvent" mean a solvent inert under the conditions of the reaction being described in conjunction therewith [including, for example, benzene, toluene, acetonitrile, tetrahydrofuran ("THF"), dimethylformamide ("DMF"), chloroform ( $\text{CHCl}_3$ ), methylene chloride (or dichloromethane or " $\text{CH}_2\text{Cl}_2$ "), diethyl ether, ethyl acetate, acetone, methylethyl ketone, methanol, ethanol, propanol, isopropanol, tert-butanol, dioxane, pyridine, and the like]. Unless specified to the contrary, the solvents used in the reactions of the present invention are inert solvents.

The "NMDA receptor" is a receptor which plays a role in cation transport, specifically calcium and sodium transport related to neuronal activity. NMDA receptors are located primarily in the brain and spinal cord.

It should be recognized that the NMDA receptors that participate in biological multivalent binding interactions are constrained to varying degrees by their intra- and intermolecular associations (e.g. cellular receptors may be covalently joined in a single structure, noncovalently associated in a multimeric structure, embedded in a membrane or polymeric matrix and so on) and therefore have less translational and rotational freedom than if the same cellular receptors were present as monomers in solution.

The term "library" refers to at least 3, preferably from  $10^2$  to  $10^9$  and more preferably from  $10^2$  to  $10^4$  multimeric compounds. Preferably, these compounds are prepared as a multiplicity of compounds in a single solution or reaction mixture which permits facile synthesis thereof. In one embodiment, the library of multimeric compounds can be directly assayed for multibinding

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properties. In another embodiment, each member of the library of multimeric compounds is first isolated and, optionally, characterized. This member is then assayed for multibinding properties.

5 The term "collection" refers to a set of multimeric compounds which are prepared either sequentially or concurrently (e.g., combinatorially). The collection comprises at least 2 members; preferably from 2 to  $10^9$  members and still more preferably from 10 to  $10^4$  members.

10 The term "ligand binding site" as used herein denotes the site on the NMDA receptor that recognizes a ligand domain and provides a binding partner for that ligand. The ligand binding site may be defined by monomeric or multimeric structures. This interaction may be capable of producing a unique biological effect, for example agonism, antagonism, modulatory effect and the like or may maintain an ongoing biological event.

15 "Ligand" as used herein denotes a compound that is a binding partner for the NMDA receptor and is bound thereto by complementarity. The specific region or regions of the ligand that is (are) recognized by the NMDA receptor is designated as the "ligand binding domain". A ligand may be either capable of binding to a receptor by itself, or may require the presence of one or more non-ligand components for binding (e.g.,  $\text{Ca}^{+2}$ ,  $\text{Mg}^{+2}$  or a water molecule).

20 It is further understood that the term "ligand" is not intended to be limited to compounds known to be useful as NMDA receptor binding compounds (e.g., known drugs). It should also be understood that portions of the ligand structure that are not essential for specific molecular recognition and binding activity may be varied substantially, replaced with unrelated structures and, in some cases,  
25 omitted entirely without affecting the binding interaction. The primary

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requirement for the ligand is that it has a ligand domain as defined above. Those skilled in the art will understand that the term ligand can equally apply to a molecule that is not normally associated with NMDA cellular receptor binding properties. In addition, it should be noted that ligands that exhibit marginal activity or lack useful activity as monomers can be highly active as multivalent compounds because of the benefits conferred by multi-valency. The only requirement for a ligand is that it has a ligand binding domain as defined above.

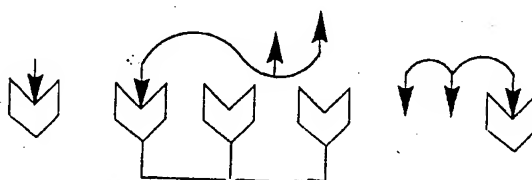
A "multimeric compound" refers to a compound that may be capable of multivalency as defined below, and which has 2 to 10 ligands covalently bound to one or more linkers which may be the same or different. The compound may or may not possess multibinding properties. At least one of the ligands comprises a ligand domain capable of binding to a NMDA receptor. The multi-binding compound provides a biological and/or therapeutic effect greater than the aggregate of unlinked ligands equivalent thereto which may be the same or different which unlinked ligands comprise a ligand domain capable of binding to NMDA receptors. That is to say that the biological and/or therapeutic effect of the ligands capable of binding to a NMDA receptor attached to the multi-binding compound is greater than that achieved by the same amount of unlinked ligands capable of binding to a NMDA receptor made available for binding to the ligand binding sites.

The phrase "increased biological or therapeutic effect" includes, for example increased affinity for a target, increased specificity for a target, increased selectivity for a target, increased potency, increased efficacy, decreased toxicity, improved duration of action, decreased side effects, increased therapeutic index, improved bioavailability, improved pharmacokinetics, improved activity spectrum, and the like. The multi-binding compounds of this invention will exhibit at least one and preferably more than one of the above mentioned effects.

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"Uni-valency" as used herein refers to a single binding interaction between one ligand as defined herein with one ligand binding site as defined herein. It should be noted that a molecule having multiple copies of a ligand (or ligands) exhibits uni-valency when only one ligand is interacting with a ligand binding site.

5 Examples of a univalent interaction are depicted below.



"Multi-valency" as used herein refers to the concurrent binding of from 2 to 10 linked ligands (which may be the same or different) and two or more corresponding ligand binding sites on the receptors which receptors may be the same or different.

10 For example, two ligands connected by a linker that bind concurrently to two ligand binding sites would be considered as bi-valency; three ligands thus connected would be an example of tri-valency. An example of tri-valency illustrating a multi-binding agent bearing three ligands versus a monovalent binding interaction is shown below:



15

univalent interaction



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trivalent interaction

It should be understood that all compounds that contain multiple copies of a ligand attached to a linker do not necessarily exhibit the phenomena of multivalency, i.e., that the biological and/or therapeutic effect of the multi-binding agent is greater than the sum of the aggregate of unlinked ligands made available to the ligand binding site. For multivalency to occur, the ligands that are connected by a linker have to be presented to their receptors by the linker in a specific manner in order to bring about the desired ligand-orienting result, and thus produce a multi-binding agent.

"Potency" as used herein refers to the minimum concentration at which a ligand is able to achieve a desirable biological or therapeutic effect. The potency of a ligand is typically proportional to its affinity for its ligand binding site. In some cases the potency may be non-linearly correlated with its affinity. In comparing the potency of two drugs, e.g., a multi-binding agent and the aggregate of its unlinked ligand, the dose-response curve of each is determined under identical test conditions (e.g. an *in vitro* or *in vivo* assay, in an appropriate animal model such as a human patient). The finding that the multi-binding agent produces an equivalent biological or therapeutic effect at a lower concentration than the aggregate unlinked ligand (e.g. on a per weight, per mole or per ligand basis) is indicative of enhanced potency.

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“Selectivity” or “specificity” is a measure of the binding preferences of a ligand for different ligand binding sites. The selectivity of a ligand with respect to its target ligand binding site relative to another ligand binding site is given by the ratio of the respective values of  $K_d$  (i.e., the dissociation constants for each ligand-receptor complex) or in cases where a biological effect is observed below the  $K_d$ , the ratio of the respective  $EC_{50}$ s (i.e., the concentrations that produce 50% of the maximum response for the ligand interacting with the two distinct ligand binding sites).

The terms “agonism” and “antagonism” are well known in the art. The term “modulatory effect” refers to the ability of the ligand to change the activity of an agonist or antagonist through binding to a ligand binding site.

The term “partial agonist” refers to a receptor agonist which cannot fully elicit a maximal response when it binds to the receptor, no matter how high the concentration of the partial agonist. A partial agonist is able to combine with the receptor, but the full effect of the binding is not elicited. This term is well known in the art and a discussion of it may be found in Textbook of Receptor Pharmacology, ch 1.4, J. Foreman and T. Johansen eds., CRC Press, 1996.

The term “treatment” refers to the treatment of pain in a mammal, particularly a human, and includes:

- (i) modulating the activity of the NMDA receptor;
- (ii) alleviating pain or lessening pain; and
- (iii) inhibiting pain.

The term “therapeutically effective amount” refers to that amount of multi-binding compound which is sufficient to effect treatment, as defined above, when administered to a mammal in need of such treatment. The therapeutically effective

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amount will vary depending upon the subject and disease condition being treated, the weight and age of the subject, the severity of the disease condition, the manner of administration and the like, which can readily be determined by one of ordinary skill in the art.

5           The term "linker," identified where appropriate by the symbol "X", refers to a group or groups that covalently link(s) from 2 to 10 ligands (as identified above) in a manner that provides for a compound capable of multi-valency when in the presence of at least one cellular receptor having 2 or more ligand binding sites. The linker is a ligand-orienting entity which may be chiral or achiral that permits  
10 attachment of multiple copies of a ligand (which may be the same or different) thereto. In some cases the linker may be biologically active. The term linker does not, however, extend to cover solid inert supports such as beads, glass particles, fibers and the like. But it is to be understood that the multi-binding compounds of this invention can be attached to a solid support if desired, for example, for use in  
15 separation and purification processes and for similar applications.

          The ligands and linkers which comprise the multibinding agents of the invention and the multibinding compounds themselves may have various stereoisomeric forms, including enantiomers and diastereomers. It is to be understood that the invention contemplates all possible stereoisomeric forms of  
20 multibinding compounds, and mixtures thereof.

          The extent to which multivalent binding is realized depends upon the efficiency with which the linker or linkers that joins the ligands presents them to their ligand binding sites on one or more receptors. Beyond presenting ligands for multivalent interactions with ligand binding sites, the linker spatially constrains  
25 these interactions to occur within dimensions defined by the linker. Thus the structural features of the linker (valency, geometry, orientation, size, flexibility,

chemical composition) are features of multivalent compounds that play an important role in determining their activities.

### Methodology

5       The linker, when covalently attached to the ligands, provides a biocompatible, substantially non-immunogenic multi-binding compound of this invention. The biological activity of the multi-binding compound is highly sensitive to the valency, geometry, composition, size, flexibility or rigidity, etc. of the linker as well as the presence or absence of anionic or cationic charge, the relative hydrophobicity/hydrophilicity of the linker, and the like on the linker. In  
10       general, the linker may be chosen from any organic molecule construct that orients two or more ligands to the receptors to permit multi-valency. In this regard, the linker can be considered as a "framework" on which the ligands are arranged in order to bring about the desired ligand-orienting result, and thus produce a multi-binding compound.

15       Ancillary groups which enhance the water solubility/hydrophilicity of the linker and, accordingly, the resulting multi-binding compounds are useful in practicing this invention. Thus, it is within the scope of the present invention to use ancillary groups such as, for example, poly(ethylene glycols), alcohols, polyols, (e.g., glycerin, glycerol propoxylate, saccharides, including mono-,  
20       oligo- and polysaccharides, etc.) carboxylates, polycarboxylates, (e.g., polyglutamic acid, polyacrylic acid, etc.), amines, polyamines, (e.g., polylysine, poly(ethyleneimine), and the like) to enhance the water solubility and/or hydrophilicity of the multi-binding compounds of this invention. In preferred  
embodiments, the ancillary group used to improve water solubility/hydrophilicity  
25       will be a polyether. In particularly preferred embodiments, the ancillary group will be a poly(ethylene glycol).

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The incorporation of lipophilic ancillary groups within the structure of the linker to enhance the lipophilicity and/or hydrophobicity of the multi-binding compounds described herein is within the scope of this invention. Lipophilic groups useful with the linkers of this invention include, by way of example only, aryl and heteroaryl groups which, as above, may be either unsubstituted or substituted with other groups, but are at least substituted with a group which allows their covalent attachment to the linker. Other lipophilic groups useful with the linkers of this invention include fatty acid derivatives which do not form bilayers in aqueous medium until higher concentrations are reached.

Also within the scope of this invention is the use of ancillary groups which result in the multi-binding compound being incorporated into a vesicle such as a liposome or a micelle. The term "lipid" refers to any fatty acid derivative that is capable of forming a bilayer such that a hydrophobic portion of the lipid material orients toward the bilayer while a hydrophilic portion orients toward the aqueous phase. Hydrophilic characteristics derive from the presence of phosphato, carboxylic, sulfato, amino, sulfhydryl, nitro and other like groups well known in the art. Hydrophobicity could be conferred by the inclusion of groups that include, but are not limited to, long chain saturated and unsaturated aliphatic hydrocarbon groups of up to 20 carbon atoms and such groups substituted by one or more aryl, heteroaryl, cycloalkyl, and/or heterocyclic group(s). Preferred lipids are phosphoglycerides and sphingolipids, representative examples of which include phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, phosphatidic acid, palmitoyleoyl phosphatidylcholine, lysophosphatidylcholine, lysophosphatidyl-ethanolamine, dipalmitoylphosphatidylcholine, dioleoylphosphatidylcholine, distearoyl-phosphatidylcholine or dilinoleoylphosphatidylcholine could be used. Other compounds lacking phosphorus, such as sphingolipid and glycosphingolipid families are also within the group designated as lipid. Additionally, the

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amphipathic lipids described above may be mixed with other lipids including triglycerides and sterols.

The flexibility of the linker can be manipulated by the inclusion of ancillary groups which are bulky and/or rigid. The presence of bulky or rigid groups can hinder free rotation about bonds in the linker or bonds between the linker and the ancillary group(s) or bonds between the linker and the functional groups. Rigid groups can include, for example, those groups whose conformational lability is restrained by the presence of rings and/or multiple bonds, for example, aryl, heteroaryl, cycloalkyl and heterocyclic groups. Other groups which can impart rigidity include polypeptide groups such as oligo- or polyproline chains.

Rigidity can also be imparted electrostatically. Thus, if the ancillary groups are either positively or negatively charged, the similarly charged ancillary groups will force the presenter linker into a configuration affording the maximum distance between each of the like charges. The energetic cost of bringing the like-charged groups closer to each other will tend to hold the linker in a configuration that maintains the separation between the like-charged ancillary groups. Further ancillary groups bearing opposite charges will tend to be attracted to their oppositely charged counterparts and potentially may enter into both inter- and intramolecular ionic bonds. This non-covalent mechanism will tend to hold the linker into a conformation which allows bonding between the oppositely charged groups. The addition of ancillary groups which are charged, or alternatively, bear a latent charge when deprotected, following the addition to the linker, include deprotection of a carboxyl, hydroxyl, thiol or amino protecting group, by a change in pH, oxidation, reduction or other mechanisms known to those skilled in the art, is within the scope of this invention.

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Bulky groups can include, for example, large atoms, ions (e.g., iodine, sulfur, metal ions, etc.) or groups containing large atoms, polycyclic groups, including aromatic groups, non-aromatic groups and structures incorporating one or more carbon-carbon multiple bonds (i.e., alkenes and alkynes). Bulky groups  
5 can also include oligomers and polymers which are branched- or straight-chain species. Species that are branched are expected to increase the rigidity of the structure more per unit molecular weight gain than are straight-chain species.

In preferred embodiments, rigidity is imparted by the presence of cyclic groups (e.g., aryl, heteroaryl, cycloalkyl, heterocyclic, etc.). In still further  
10 preferred embodiments, the ring is an aryl group such as, for example, phenyl or naphthyl. In other preferred embodiments, the linker comprises one or more six-membered rings or crown groups which, while not rigid, retain the conformation of the linker through conformational entropy.

In view of the above, it is apparent that the appropriate selection of a linker  
15 group providing suitable orientation, entropy and physico-chemical properties is well within the skill of the art. Eliminating or reducing antigenicity of the multi-binding compounds described herein is also within the scope of this invention.

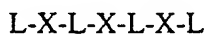
As explained above, the multi-binding compounds described herein  
comprise 2-10 ligands for the NMDA receptor attached to a linker that links the  
20 ligands in such a manner that they are presented to the NMDA receptor complex for multivalent interactions. The linker spatially constrains these interactions to occur within dimensions defined by the linker, thus greatly increasing biological activity of the multi-binding compound as compared to the same number of ligands used in mono-binding form.

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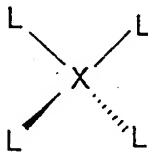
The multi-binding compounds of this invention are preferably represented by the empirical formula  $(L)_p(X)_q$  where L, X,  $p$  and  $q$  are as defined above. This is intended to include the several ways in which the ligands can be linked together in order to achieve the objective of multi-valency, and a more detailed explanation is described below.

As noted previously, the linker may be considered as a framework to which ligands are attached. Thus, it should be recognized that the ligands can be attached at any suitable position on this framework, for example, at the termini of a linear chain or at any intermediate position.

The simplest and most preferred multi-binding compound is a bivalent compound which can be represented as L-X-L, where L is a ligand and is the same or different and X is the linker. A trivalent compound could also be represented in a linear fashion, i.e., as a sequence of repeated units L-X-L-X-L, in which L is a ligand and is the same or different at each occurrence, as can X. However, a trimer can also be a multi-binding compound comprising three ligands attached to a central core, and thus represented as  $(L)_3X$ , where the linker X could include, for example, an aryl or cycloalkyl group. Tetravalent compounds can be represented as, for example, in a linear array:



or in a tetrahedral array:



where X and L are as defined herein.

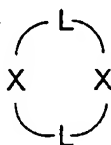


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The same considerations apply to higher multibinding compounds of this invention containing 5-10 ligands. However, for multibinding agents attached to a central linker such as aryl or cycloalkyl, there is a self-evident constraint that there must be sufficient attachment sites on the linker to accommodate the number of

5 ligands present; for example, a benzene ring could not directly accommodate more than 6 ligands, whereas a multi-ring linker (e.g., biphenyl) could accommodate a larger number of ligands.

Certain of the above described compounds may alternatively be represented as cyclic chains of the form:



10 and variants thereof.

All of the above variations are intended to be within the scope of the invention defined by the formula  $(L)_p(X)_q$ .

In view of the above description of the linker, it is understood that the term "linker" when used in combination with the term "multibinding compound"

15 includes both a covalently contiguous single linker (e.g., L-X-L) and multiple covalently non-contiguous linkers (L-X-L-X-L) within the multibinding compound.

#### Preparation of Multibinding Compounds

The multibinding compounds of this invention can be prepared from readily available starting materials using the following general methods and procedures. It

20 will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are

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given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

5           Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. The choice of a suitable protecting group for a particular functional group as well as suitable conditions for protection and deprotection are well known in the art. For example, numerous protecting groups,  
10           and their introduction and removal, are described in T. W. Greene and G. M. Wuts, *Protecting Groups in Organic Synthesis*, Second Edition, Wiley, New York, 1991, and references cited therein.

          Any compound which acts as a ligand toward the NMDA receptor can be used as a ligand in this invention. It is desirable that the ligand or ligands be  
15           antagonists or partial agonists in order to modulate the activity of the NMDA receptor to lessen or alleviate conditions such as pain sensation, Alzheimer's, cognitive disorder, dementia, schizophrenia, ocular disease, AIDS-related complex, peripheral neuropathy, CV ischemia, infarction, stroke, motor neuron disease, epilepsy, seizure, convulsions, neurodegenerative disease, micturition  
20           disorders, migraine, Parkinson's disease, psychosis, Huntingdon's chorea and cardiac failure, wherein such compounds do not have the neurotoxic effects associated with current NMDA receptor noncompetitive binding compounds. In particular, a treatment for pain sensation is desirable as pain is a common effect associated with many of the above described conditions.

25           Of the many possible binding sites of the NMDA receptor, only a few are desirable for modulation of the receptor. As described in Kemp et al., Drugs

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Pharm. Sci. (1998) Vol. 89 (Receptor based Drug Design) pp. 297-321, many of the possible ligand-binding receptors have unwanted side effects. For example, ion channel blockers are too effective in that they have a high affinity for the cationic channel once it is opened, and have a low rate of reversibility. Therefore, once bound, the ion channel blocker is not easily removed, and therefore always blocks the receptor. This is known to cause behavioral, cardiovascular and cytotoxic effects. Similarly, antagonistic binding of the glutamate site would prevent all activity of the receptor. Bonding of a polyamine affects many different functions, including potassium transport, calcium transport, AMPA and the functioning of kinate receptors.

In contrast, antagonistic or partial agonist glycine ligands would modulate the activity of the receptor without entirely preventing the receptor from functioning, as glycine is known to act in a modulatory capacity. Also, as discussed elsewhere herein, subtype specific ligands would affect only certain NMDA receptors, leaving others to function, thereby alleviating some of the side effects currently known to occur with non-subtype specific NMDA receptor antagonists. Similar results may be seen with the use of redox site ligands.

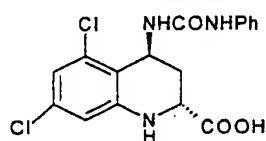
Therefore, ligands which are glycine antagonists or partial agonists or subtype specific antagonists or partial agonists are particularly desirable. As discussed in further detail below, numerous such ligands are known in the art and any of these known compounds or derivatives thereof may be employed as ligands in this invention. Such known ligands are now further described.

Many glycine antagonists, glycine partial agonists, glutamate antagonists, polyamines, ion channel blockers and redox site binders are known for binding to the NMDA receptor. Examples of such ligands are shown below, as well as other ligands which may fall into one or more of the above described categories.

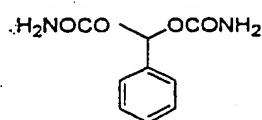
-47-

Ligands of the respective categories are referred to herein as ligands L-1 through L-7, wherein each of L-1, L-2, L-3, L-4, L-5, L-6 and L-7 represent a class of compounds, including derivatives thereof, as described above.

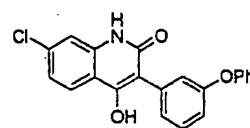
### Glycine Antagonists:



L 689560



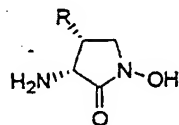
felbamate



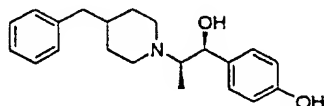
L-701324

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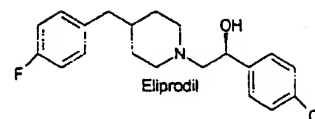
### Glycine Partial Agonists:



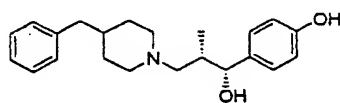
R=H; HA 966  
R=Me; L687414



ifenprodil



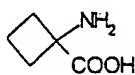
Eliprodil



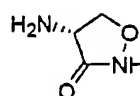
RO-25-6981



Nyldrin



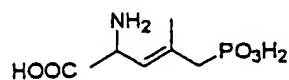
SYM 2030



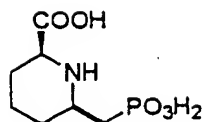
cycloserine

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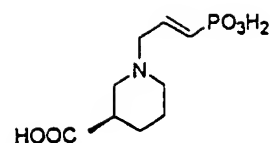
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**Glutamate Antagonists:**

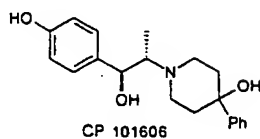
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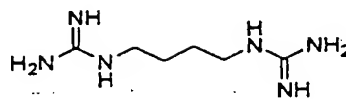
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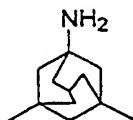
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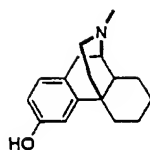
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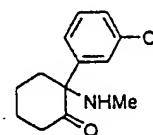
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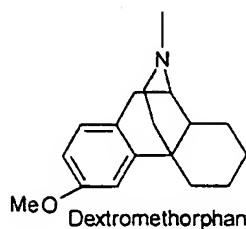
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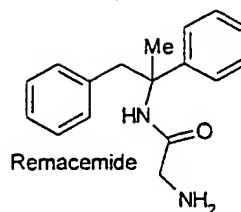
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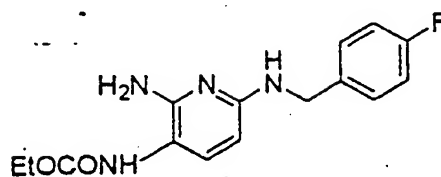
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Dextromethorphan



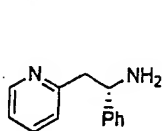
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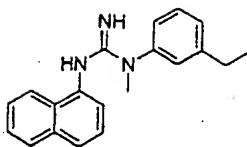
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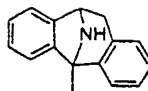
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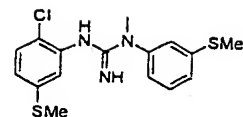
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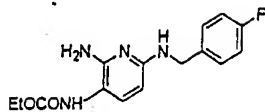
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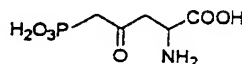
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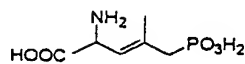
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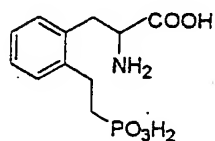
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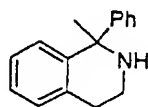
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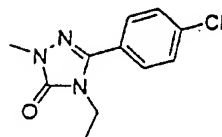
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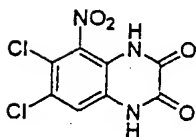
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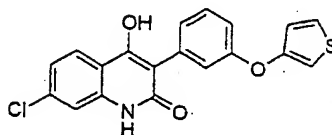
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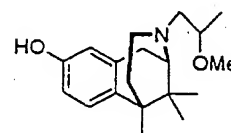
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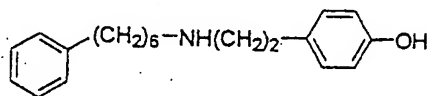
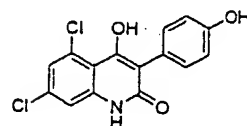
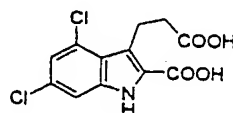
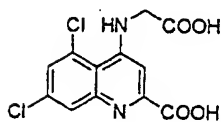
licostinel



L-705022



BIII 227Cl



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In particular, ligands of the above types L-1 through L-7 may comprise one or more of the following compounds: L-689560, felbamate, L-701324, HA 966, L-687414, ifenprodil, eliprodil, RO-25-6981, nylidrin, SYM 2030, cycloserine, CGP-37489, CP-101606, arcaine, memantidine, dextrophan, detromethorphan, remacemide, ketamine, ARL 15896AR, aptiganel, MK801, CNS-5161, selfotel, flupertine, SDZ EAA 494, ketobemidone, MDL 10043, CGP-40116, NPC 12626, FR 115427, MDL 27266, licostinel, L-705022, and BIII 227Cl. Other NMDA receptor ligands and derivatives may be known to those in the art. Preferentially, NMDA receptor ligands or derivatives thereof used in the invention are bound to only the NMDA receptor.

Further ligands which may be used in a compound of the invention as described herein may include, for example, other known NMDA receptor ligands such as dexanabinol, midafotel, RO-24-6173, RO-8-4304, GPI-3000, ADCI, FPL-16283, LY-274614, WAY-126090, HO-473, CNS-1531, CP-98113, ES-2421, CNS-1044, CNS-5065, CNS-1118, CNS-1524, CNS-1505, L-701315, L-701376, L-701252, L-698532, L-687414, L-701273, LY-235959, LY-233053, LY-235723, LY-233536, EMD-95885, CGP-39653, MRZ-2/579, CP-101616, AP-6, NC-1210, PD-158473, NPS-1506 and derivatives or analogs thereof.

The ligands may be bound together in any combination by a linker, as described herein. Therefor, any ligand capable of binding to an NMDA receptor, such as a glycine antagonist, glycine partial agonist, glutamate antagonist, polyamine, ion channel blocker or redox site binder may be combined with one or more glycine antagonist, glycine partial agonist, glutamate antagonist, polyamine, ion channel blocker or redox site binder to form a compound of the invention. For example, a glycine antagonist ligand may be joined by one or more linkers to one or more ligands selected from a glycine antagonist, glycine partial agonist, glutamate antagonist, polyamine, ion channel blocker and redox site binder. A

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glycine partial agonist may be joined by one or more linkers to one or more ligands selected from a glycine antagonist, glycine partial agonist, glutamate antagonist, polyamine, ion channel blocker and redox site binder. A glutamate antagonist may be joined by one or more linkers to one or more ligands selected from a glycine antagonist, glycine partial agonist, glutamate antagonist, polyamine, ion channel blocker and redox site binder. A polyamine may be joined by one or more linkers to one or more ligands selected from a glycine antagonist, glycine partial agonist, glutamate antagonist, polyamine, ion channel blocker and redox site binder. An ion channel blocker may be joined by one or more linkers to one or more ligands selected from a glycine antagonist, glycine partial agonist, glutamate antagonist, polyamine, ion channel blocker and redox site binder. A redox site binder may be joined by one or more linkers to one or more ligands selected from a glycine antagonist, glycine partial agonist, glutamate antagonist, polyamine, ion channel blocker and redox site binder. Other NMDA antagonists, partial agonists or agonists as known in the art may also be bound by one or more linkers to one or more ligands selected from a glycine antagonist, glycine partial agonist, glutamate antagonist, polyamine, ion channel blocker and redox site binder.

#### Combinatorial Libraries

Combinatorial approaches for identifying multimeric compounds which possess multibinding properties will now be discussed.

Specifically, factors such as the proper juxtaposition of the individual ligands of a multibinding compound with respect to the relevant array of binding sites on a target or targets is important in optimizing the interaction of the multibinding compound with its target(s) and to maximize the biological advantage through multivalency. One approach is to identify a library of candidate multibinding compounds with properties spanning the multibinding parameters that



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are relevant for a particular target. These parameters include: (1) the identity of ligand(s), (2) the orientation of ligands, (3) the valency of the construct, (4) linker length, (5) linker geometry, (6) linker physical properties, and (7) linker chemical functional groups.

5            Libraries of multimeric compounds potentially possessing multibinding properties (i.e., candidate multibinding compounds) and comprising a multiplicity of such variables are prepared and these libraries are then evaluated via conventional assays corresponding to the ligand selected and the multibinding parameters desired. Considerations relevant to each of these variables are set  
10    forth below.

#### Selection of ligand(s)

A single ligand or set of ligands is (are) selected for incorporation into the libraries of candidate multibinding compounds which library is directed against a particular biological target or targets. The only requirement for the ligands chosen  
15    is that they are capable of interacting with the selected target(s). Thus, ligands may be known drugs, modified forms of known drugs, substructures of known drugs or substrates of modified forms of known drugs (which are competent to interact with the target), or other compounds. Ligands are preferably chosen based on known favorable properties that may be projected to be carried over to or  
20    amplified in multibinding forms. Favorable properties include demonstrated safety and efficacy in human patients, ability to increase insulin sensitivity, ability to lower serum triglyceride, cholesterol and/or fatty acid levels, etc. However, it is crucial to note that ligands which display an unfavorable property from among the previous list may obtain a more favorable property through the process of  
25    multibinding compound formation; i.e., ligands should not necessarily be excluded on such a basis. For example, a ligand that is not sufficiently potent at a particular target so as to be efficacious in a human patient may become highly potent and

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efficacious when presented in multibinding form. A ligand that is potent and efficacious but not of utility because of a non-mechanism-related toxic side effect may have increased therapeutic index (increased potency relative to toxicity) as a multibinding compound. Compounds that exhibit short *in vivo* half-lives may have extended half-lives as multibinding compounds. Physical properties of ligands that limit their usefulness (e.g. poor bioavailability due to low solubility, hydrophobicity, hydrophilicity) may be rationally modulated in multibinding forms, providing compounds with physical properties consistent with the desired utility.

10    Orientation: selection of ligand attachment points and linking chemistry

Several points are chosen on each ligand at which to attach the ligand to the linker. The selected points on the ligand/linker for attachment are functionalized to contain complementary reactive functional groups. This permits probing the effects of presenting the ligands to their receptor(s) in multiple relative orientations, an important multibinding design parameter. The only requirement for choosing attachment points is that attaching to at least one of these points does not abrogate activity of the ligand. Such points for attachment can be identified by structural information when available. Alternatively, evaluation of ligand/target binding by nuclear magnetic resonance will permit the identification of sites non-essential for ligand/target binding. See, for example, Fesik, et al., U.S. Patent No. 5,891,643. When such structural information is not available, utilization of structure-activity relationships (SAR) for ligands will suggest positions where substantial structural variations are, and are not allowed. In the absence of both structural and SAR information, a library is merely selected with multiple points of attachment to allow presentation of the ligand in multiple distinct orientations. Subsequent evaluation of this library will indicate what positions are suitable for attachment.

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It is important to emphasize that positions of attachment that do abrogate the activity of the monomeric ligand may also be advantageously included in candidate multibinding compounds in the library provided that such compounds bear at least one ligand attached in a manner which does not abrogate intrinsic activity. This selection derives from, for example, heterobivalent interactions within the context of a single target molecule. For example, consider a receptor antagonist ligand bound to its target receptor, and then consider modifying this ligand by attaching to it a second copy of the same ligand with a linker which allows the second ligand to interact with the same receptor molecule at sites proximal to the antagonist binding site, which include elements of the receptor that are not part of the formal antagonist binding site and/or elements of the matrix surrounding the receptor such as the membrane. Here, the most favorable orientation for interaction of the second ligand molecule with the receptor/matrix may be achieved by attaching it to the linker at a position which abrogates activity of the ligand at the formal antagonist binding site. Another way to consider this is that the SAR of individual ligands within the context of a multibinding structure is often different from the SAR of those same ligands in monomeric form.

The foregoing discussion focused on bivalent interactions of dimeric compounds bearing two copies of the same ligand joined to a single linker through different attachment points, one of which may abrogate the binding/activity of the monomeric ligand. It should also be understood that bivalent advantage may also be attained with heterodimeric constructs bearing two different ligands that bind to common or different targets. For example, a glycine antagonist and a polyamine site antagonist may be joined to a linker through attachment points which do not abrogate the binding affinity of the monomeric ligands for their respective receptor sites. The dimeric compound may achieve enhanced affinity for both receptors due to favorable interactions between the glycine ligand and elements proximal to the formal polyamine ligand binding site and between the polyamine ligand and

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elements proximal to the formal glycine ligand binding site. Thus, the dimeric compound may be a more potent and selective antagonist of the NMDA receptor and a superior therapy for pain.

Once the ligand attachment points have been chosen, one identifies the types of chemical linkages that are possible at those points. The most preferred types of chemical linkages are those that are compatible with the overall structure of the ligand (or protected forms of the ligand), readily and generally formed, stable and intrinsically innocuous under typical chemical and physiological conditions, and compatible with a large number of available linkers. Amide bonds, ethers, amines, carbamates, ureas, and sulfonamides are but a few examples of preferred linkages.

Linkers: spanning relevant multibinding parameters through selection of valency, linker length, linker geometry, rigidity, physical properties, and chemical functional groups

In the library of linkers employed to generate the library of candidate multibinding compounds, the selection of linkers employed in this library of linkers takes into consideration the following factors.

Valency. In most instances the library of linkers is initiated with divalent linkers. The choice of ligands and proper juxtaposition of two ligands relative to their binding sites permits such molecules to exhibit target binding affinities and specificities more than sufficient to confer biological advantage. Furthermore, divalent linkers or constructs are also typically of modest size such that they retain the desirable biodistribution properties of small molecules.

Linker length. Linkers are chosen in a range of lengths to allow the spanning of a range of inter-ligand distances that encompass the distance

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preferable for a given divalent interaction. In some instances the preferred distance can be estimated rather precisely from high-resolution structural information of targets, typically enzymes and soluble receptor targets. In other instances where high-resolution structural information is not available, one can  
5 make use of simple models to estimate the maximum distance between binding sites either on adjacent receptors or at different locations on the same receptor. In situations where two binding sites are present on the same target (or target subunit for multisubunit targets), preferred linker distances are 2-20 Å, with more preferred linker distances of 3-12 Å. In situations where two binding sites reside  
10 on separate (e.g., protein) target sites, preferred linker distances are 20-100 Å, with more preferred distances of 30-70 Å.

Linker geometry and rigidity. The combination of ligand attachment site, linker length, linker geometry, and linker rigidity determine the possible ways in which the ligands of candidate multibinding compounds may be displayed in three  
15 dimensions and thereby presented to their binding sites. Linker geometry and rigidity are nominally determined by chemical composition and bonding pattern, which may be controlled and are systematically varied as another spanning function in a multibinding array. For example, linker geometry is varied by attaching two ligands to the ortho, meta, and para positions of a benzene ring, or  
20 in *cis*- or *trans*-arrangements at the 1,1- vs. 1,2- vs. 1,3- vs. 1,4- positions around a cyclohexane core or in *cis*- or *trans*-arrangements at a point of ethylene unsaturation. Linker rigidity is varied by controlling the number and relative energies of different conformational states possible for the linker. For example, a divalent compound bearing two ligands joined by 1,8-octyl linker has many more  
25 degrees of freedom, and is therefore less rigid than a compound in which the two ligands are attached to the 4,4' positions of a biphenyl linker.

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Linker physical properties. The physical properties of linkers are nominally determined by the chemical constitution and bonding patterns of the linker, and linker physical properties impact the overall physical properties of the candidate multibinding compounds in which they are included. A range of linker compositions is typically selected to provide a range of physical properties (hydrophobicity, hydrophilicity, amphiphilicity, polarization, acidity, and basicity) in the candidate multibinding compounds. The particular choice of linker physical properties is made within the context of the physical properties of the ligands they join and, preferably, the goal is to generate molecules with favorable properties.

For example, linkers can be selected to avoid those that are too hydrophilic or too hydrophobic to be readily absorbed and/or distributed *in vivo*.

Linker chemical functional groups. Linker chemical functional groups are selected to be compatible with the chemistry chosen to connect linkers to the ligands and to impart the range of physical properties sufficient to span initial examination of this parameter.

#### Combinatorial synthesis

Having chosen a set of  $n$  ligands ( $n$  being determined by the sum of the number of different attachment points for each ligand chosen) and  $m$  linkers by the process outlined above, a library of  $(n!)m$  candidate divalent multibinding compounds is prepared which spans the relevant multibinding design parameters for a particular target. For example, an array generated from two ligands, one which has two attachment points (A1, A2) and one which has three attachment points (B1, B2, B3) joined in all possible combinations provide for at least 15 possible combinations of multibinding compounds:

A1-A1	A1-A2	A1-B1	A1-B2	A1-B3	A2-A2	A2-B1	A2-B2
A2-B3	B1-B1	B1-B2	B1-B3	B2-B2	B2-B3	B3-B3	

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When each of these combinations is joined by 10 different linkers, a library of 150 candidate multibinding compounds results.

Given the combinatorial nature of the library, common chemistries are preferably used to join the reactive functionalities on the ligands with  
5 complementary reactive functionalities on the linkers. The library therefore lends itself to efficient parallel synthetic methods. The combinatorial library can employ solid phase chemistries well known in the art wherein the ligand and/or linker is attached to a solid support. Alternatively and preferably, the combinatorial library is prepared in the solution phase. After synthesis, candidate multibinding  
10 compounds are optionally purified before assaying for activity by, for example, chromatographic methods (e.g., HPLC).

Analysis of array by biochemical, analytical, pharmacological, and computational methods

Various methods are used to characterize the properties and activities of the  
15 candidate multibinding compounds in the library to determine which compounds possess multibinding properties. Physical constants such as solubility under various solvent conditions and logD/clogD values are determined. A combination of NMR spectroscopy and computational methods is used to determine low-energy conformations of the candidate multibinding compounds in fluid media. The  
20 ability of the members of the library to bind to the desired target and other targets is determined by various standard methods, which include radioligand displacement assays for receptor and ion channel targets, and kinetic inhibition analysis for many enzyme targets. *In vitro* efficacy, such as for receptor agonists and antagonists, ion channel blockers, and antimicrobial activity are also  
25 determined. Pharmacological data, including oral absorption, everted gut penetration, other pharmacokinetic parameters and efficacy data are determined in

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appropriate models. In this way, key structure-activity relationships are obtained for multibinding design parameters which are then used to direct future work.

The members of the library which exhibit multibinding properties, as defined herein, can be readily determined by conventional methods. First, those members which exhibit multibinding properties are identified by conventional methods as described above, including conventional assays (both *in vitro* and *in vivo*).

Second, ascertaining the structure of those compounds which exhibit multibinding properties can be accomplished via art recognized procedures. For example, each member of the library can be encrypted or tagged with appropriate information allowing determination of the structure of relevant members at a later time. See, for example, Dower, et al., International Patent Application Publication No. WO 93/06121; Brenner, et al., Proc. Natl. Acad. Sci., USA, 89:5181 (1992); Gallop, et al., U.S. Patent No. 5,846,839; each of which is incorporated herein by reference in its entirety. Alternatively, the structure of relevant multivalent compounds can also be determined from soluble and untagged libraries of candidate multivalent compounds by methods known in the art, such as those described by Hindsgaul, et al., Canadian Patent Application No. 2,240,325 which was published on July 11, 1998. Such methods couple frontal affinity chromatography with mass spectroscopy to determine both the structure and relative binding affinities of candidate multibinding compounds to receptors.

The process set forth above for dimeric candidate multibinding compounds can, of course, be extended to trimeric candidate compounds and higher analogs thereof.



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Follow-up synthesis and analysis of additional array(s)

Based on the information obtained through analysis of the initial library, an optional component of the process is to ascertain one or more promising multibinding "lead" compounds as defined by particular relative ligand orientations, linker lengths, linker geometries, etc. Additional libraries can then be generated around these leads to provide for further information regarding structure to activity relationships. These arrays typically bear more focused variations in linker structure to further optimize target affinity and/or activity at the target (antagonism, partial agonism, etc.), and/or alter physical properties. By iterative redesign/analysis using the novel principles of multibinding design along with classical medicinal chemistry, biochemistry, and pharmacology approaches, one is able to prepare and identify optimal multibinding compounds that exhibit biological advantage towards their targets and as therapeutic agents.

To further elaborate upon this procedure, suitable divalent linkers include, by way of example only, those derived from dicarboxylic acids, disulfonylhalides, dialdehydes, dipseudohalides, diketones, dihalides, diisocyanates, diamines, diols, diboronates, mixtures of carboxylic acids, sulfonylhalides, aldehydes, ketones, halides, isocyanates, amines and diols. In each case, the carboxylic acid, sulfonylhalide, aldehyde, ketone, halide, isocyanate, amine and diol functional group is reacted with a complementary functionality on the ligand to form a covalent linkage. Such complementary functionality is well known in the art as illustrated in the following table, which is exemplary only:

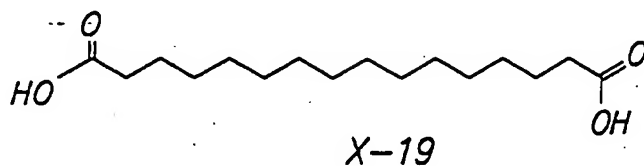
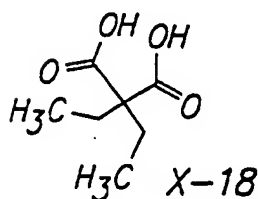
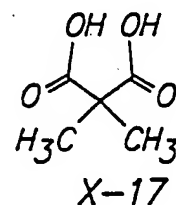
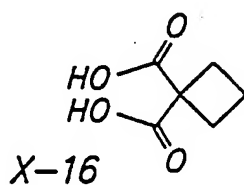
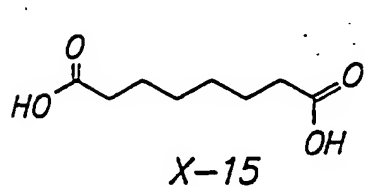
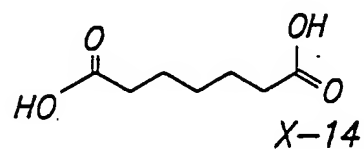
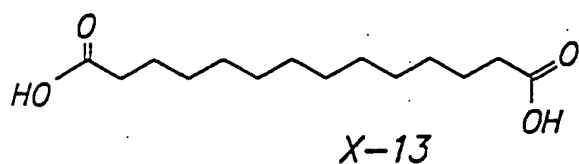
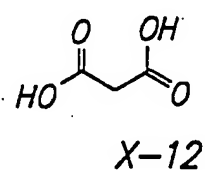
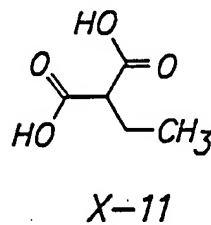
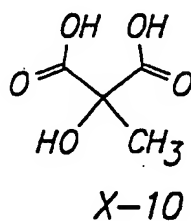
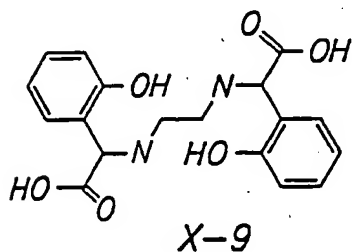
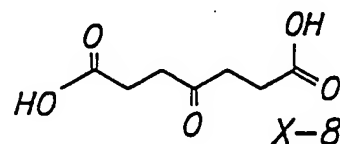
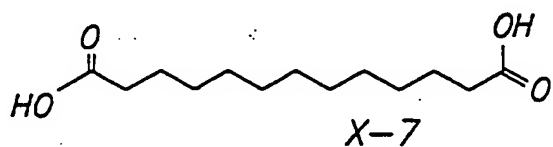
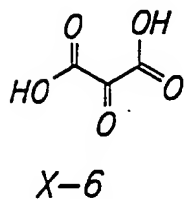
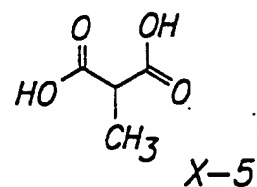
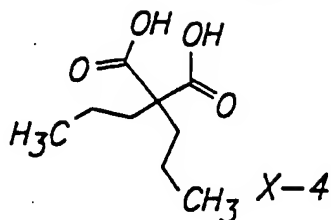
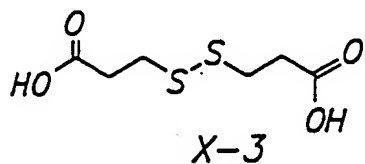
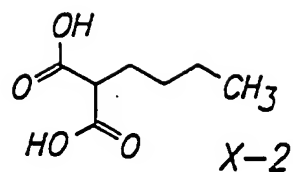
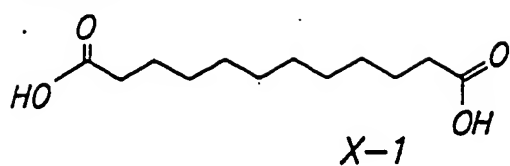
-61-

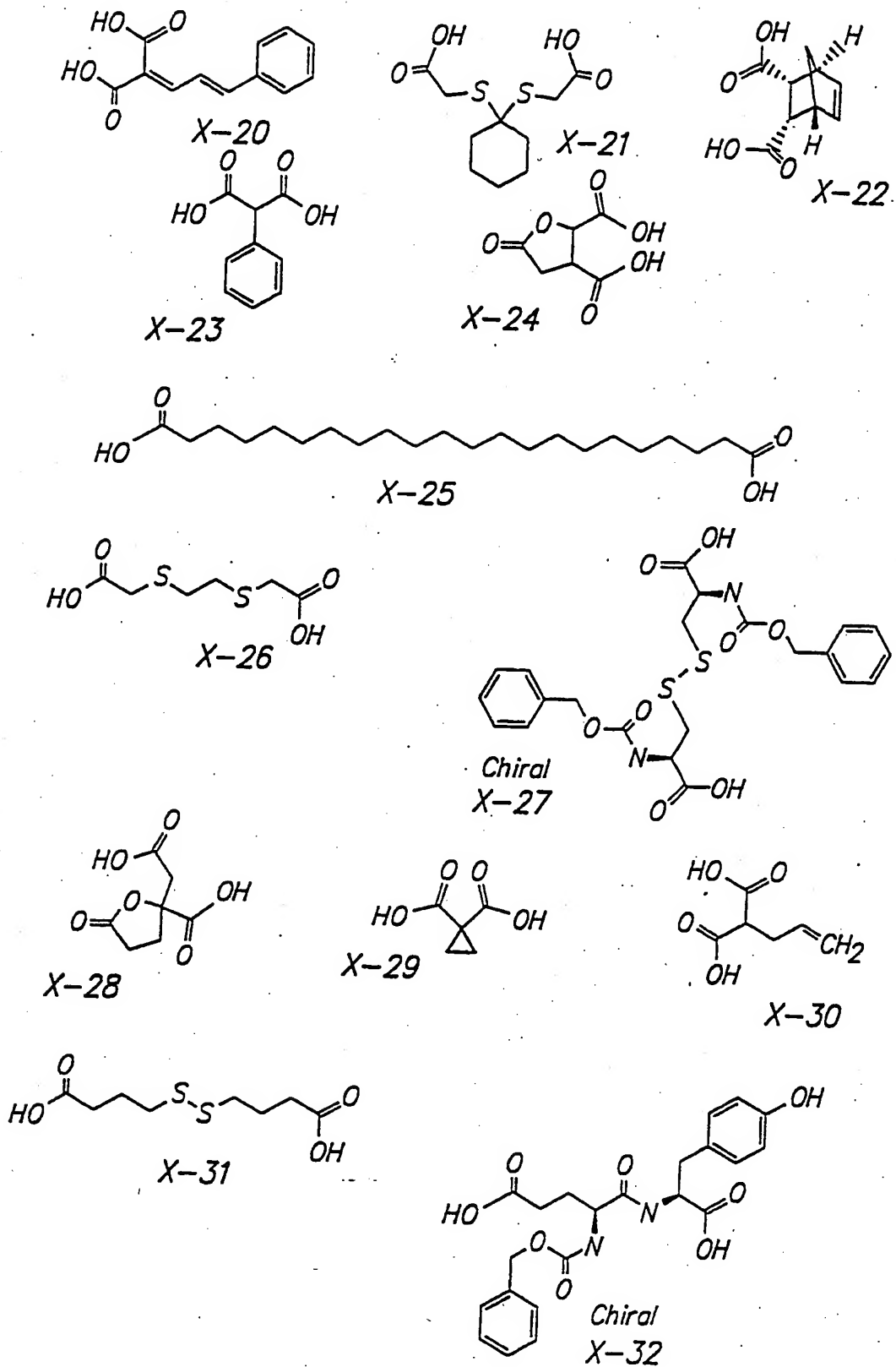
## COMPLEMENTARY BINDING CHEMISTRIES

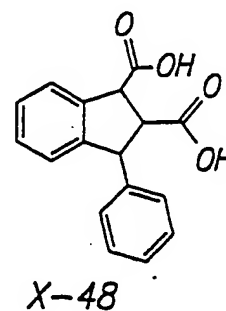
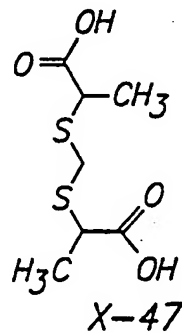
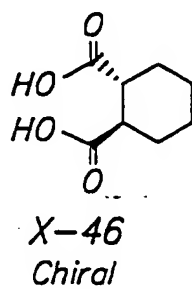
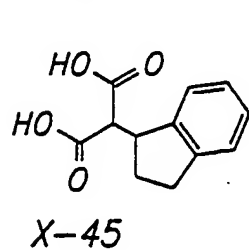
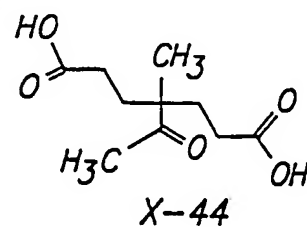
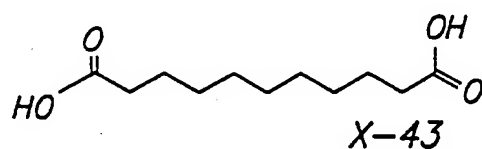
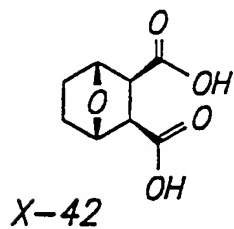
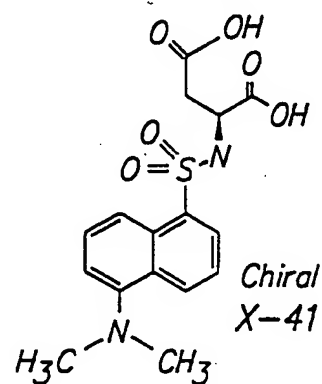
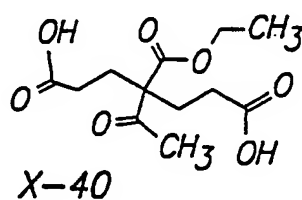
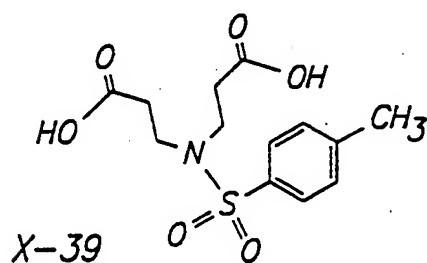
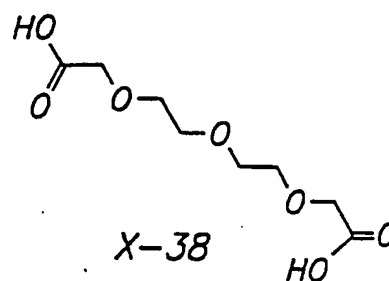
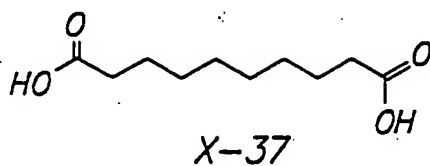
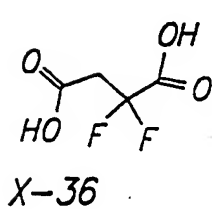
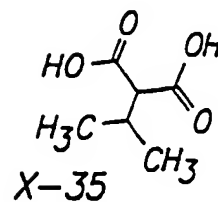
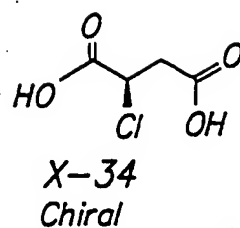
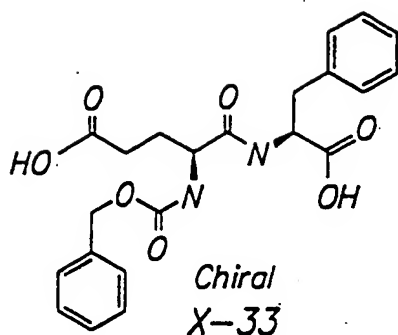
	<u>First Reactive Group</u>	<u>Second Reactive Group</u>	<u>Linkage</u>
	hydroxyl	isocyanate	urethane
	amine	epoxide	$\beta$ -hydroxyamine
5	sulfonyl halide	amine	sulfonamide
	carboxyl acid	amine	amide
	hydroxyl	alkyl/aryl halide	ether
	aldehyde	amine/ $\text{NaCNBH}_3$	amine
	ketone	amine/ $\text{NaCNBH}_3$	amine
10	amine	isocyanate	urea

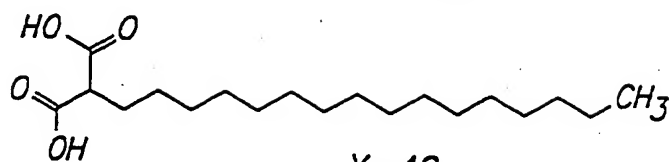
Exemplary linkers include the following linkers identified as X-1 through X-418 as set forth below in Table 1:

## Diacids

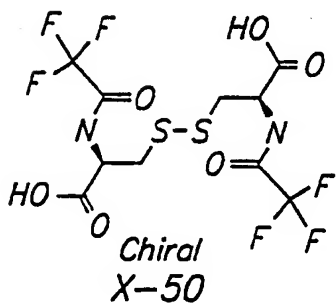
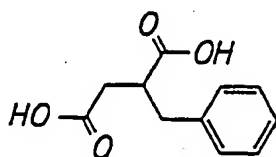




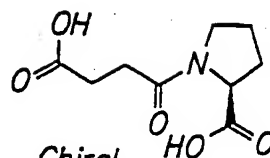
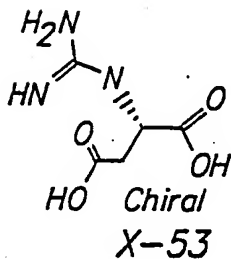
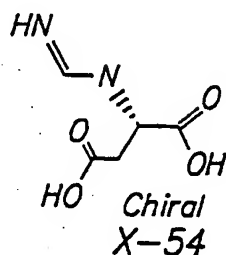
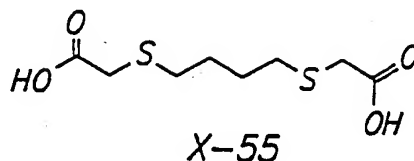




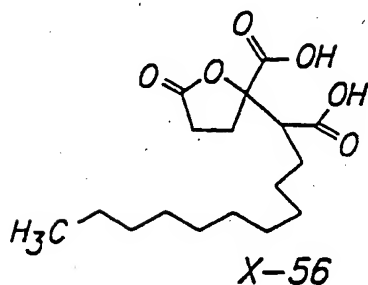
X-49

Chiral  
X-50

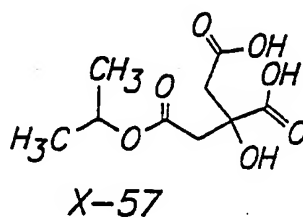
X-51

Chiral  
X-52Chiral  
X-53Chiral  
X-54

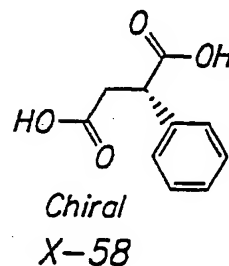
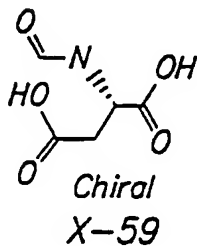
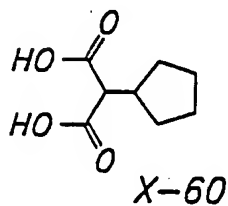
X-55



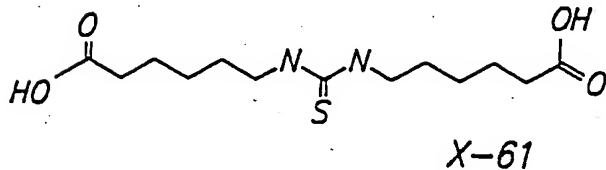
X-56



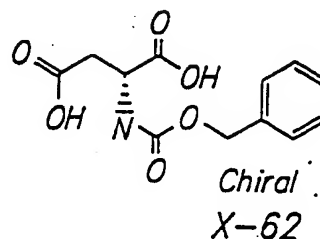
X-57

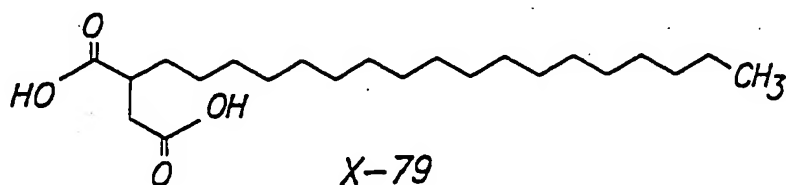
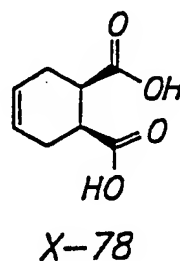
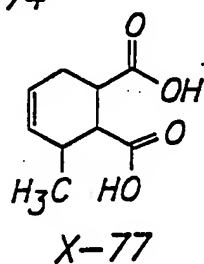
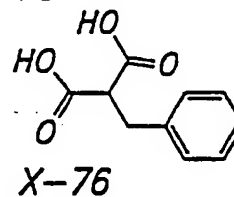
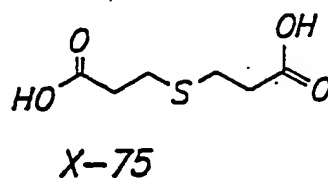
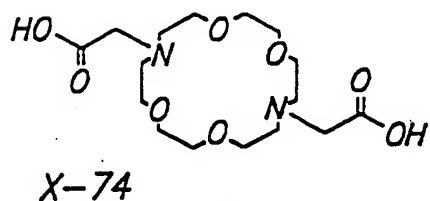
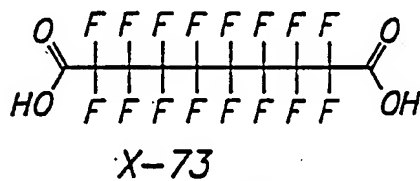
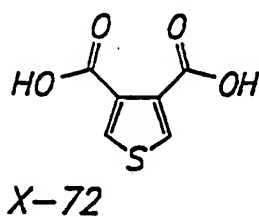
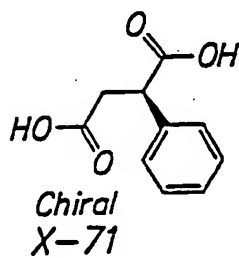
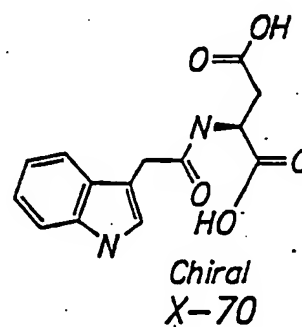
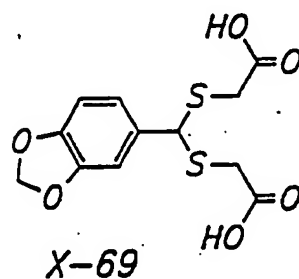
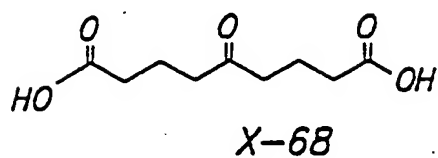
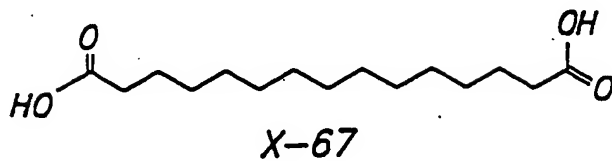
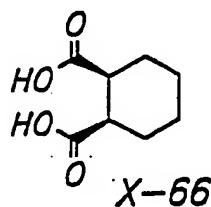
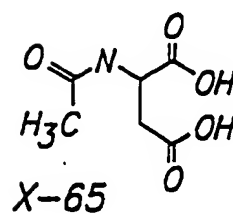
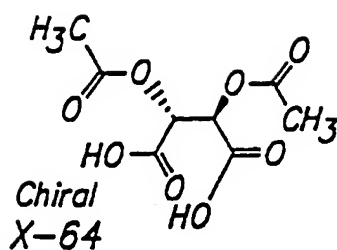
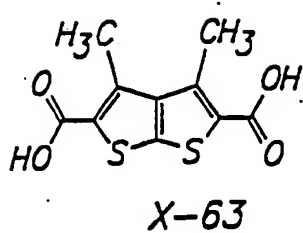
Chiral  
X-58Chiral  
X-59

X-60

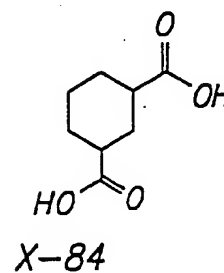
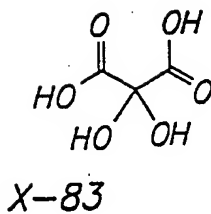
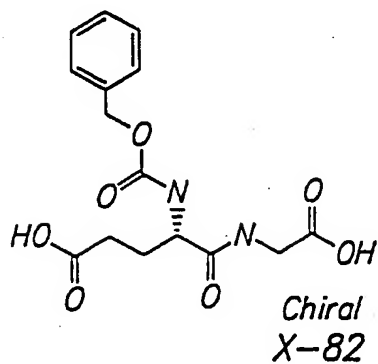
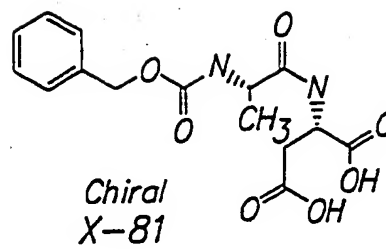
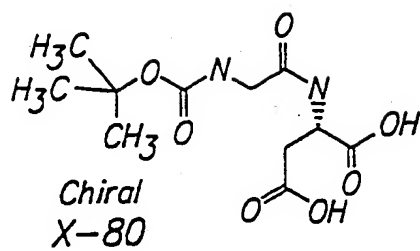


X-61

Chiral  
X-62

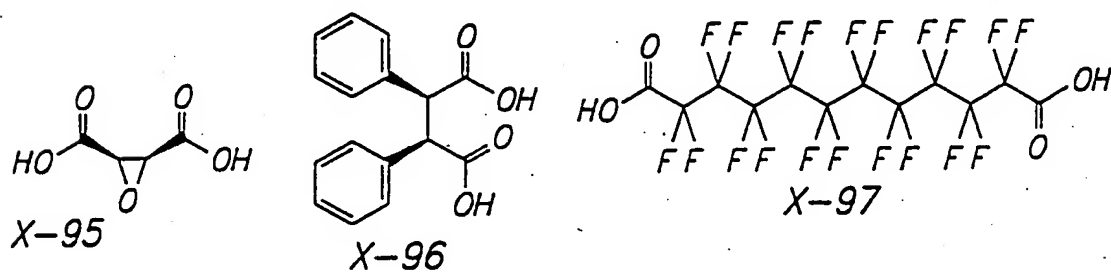
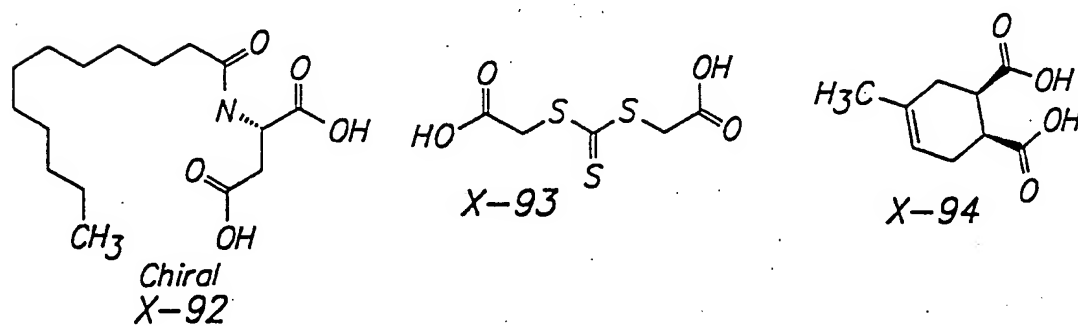
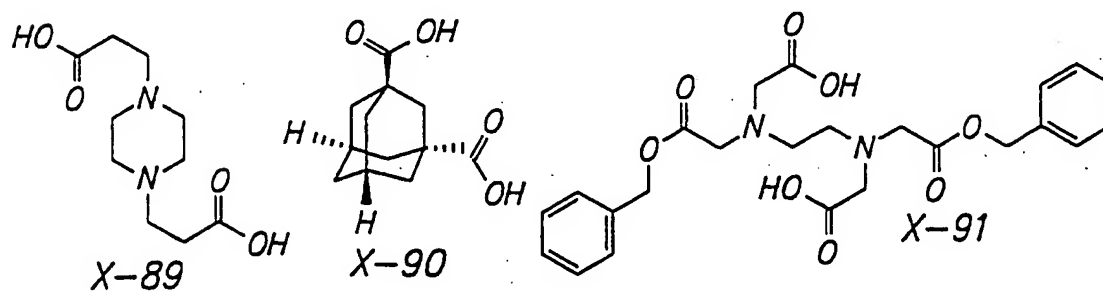
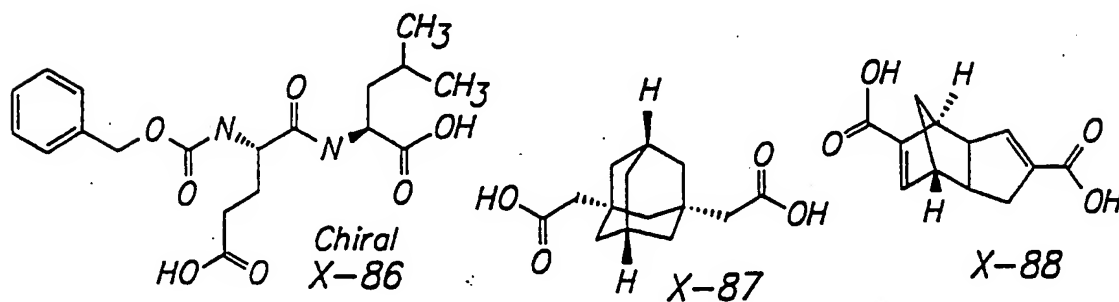
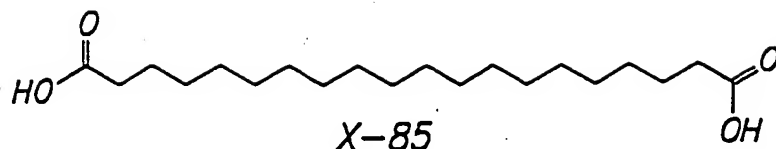


-67 (a)-

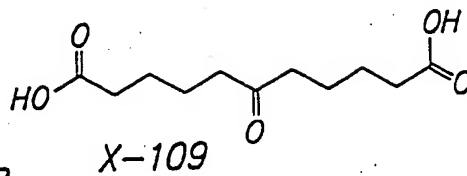
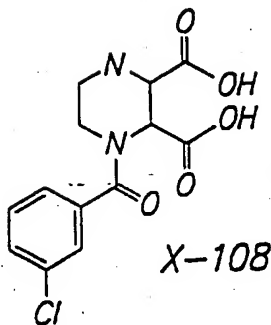
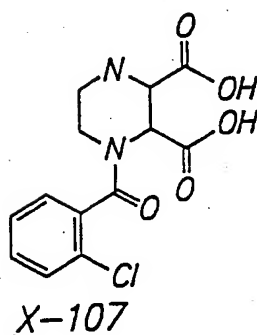
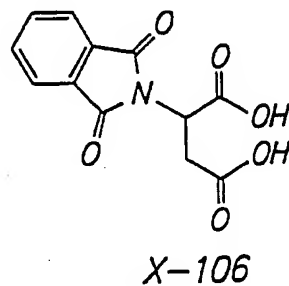
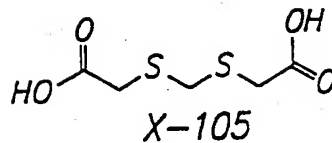
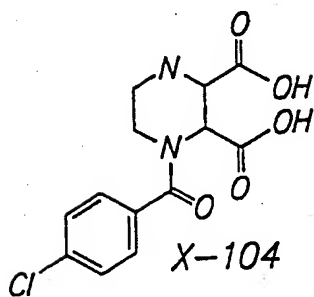
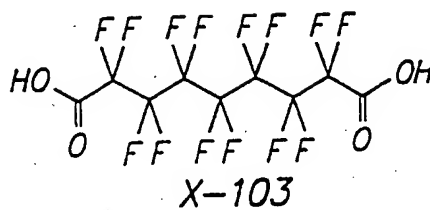
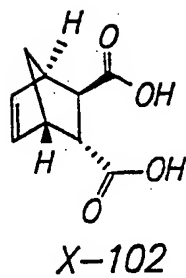
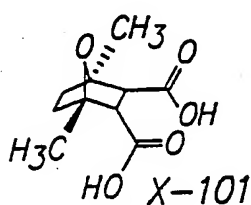
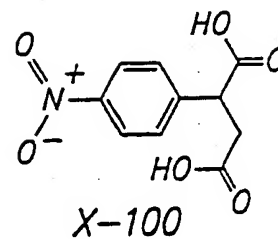
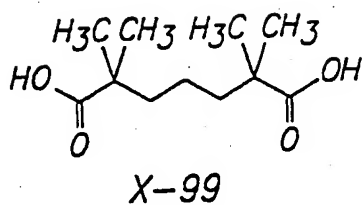
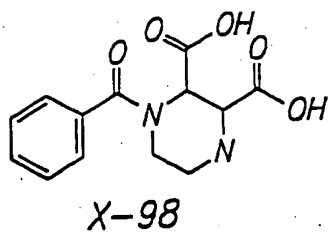




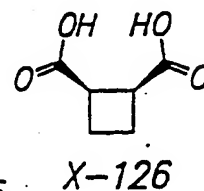
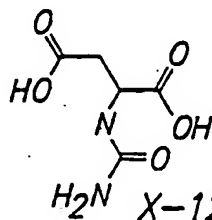
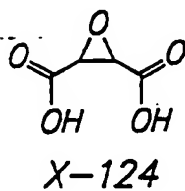
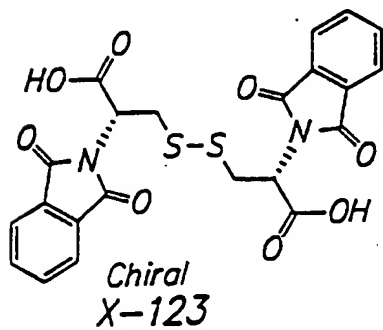
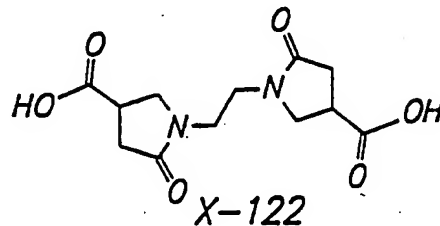
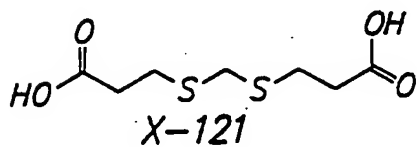
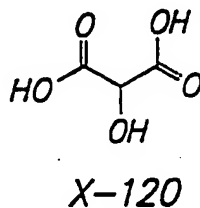
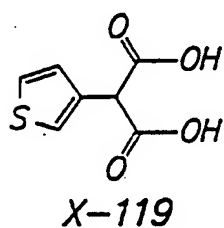
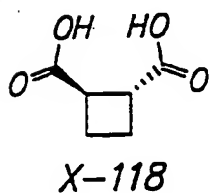
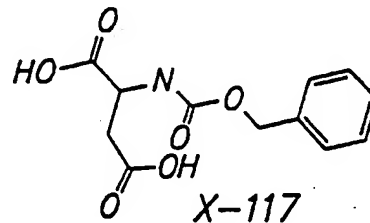
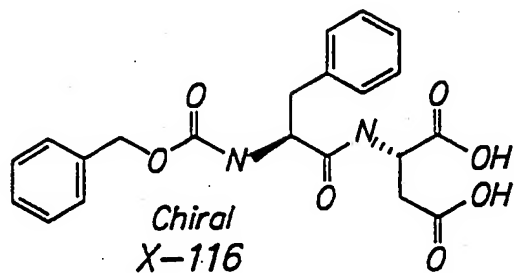
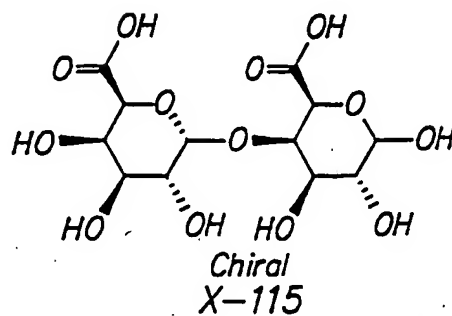
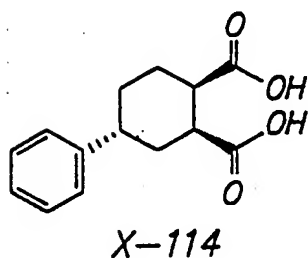
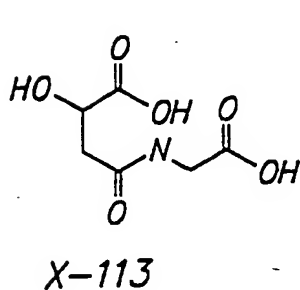
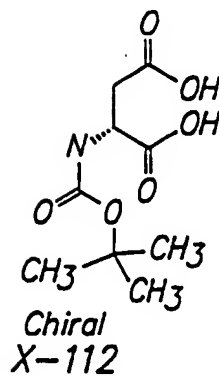
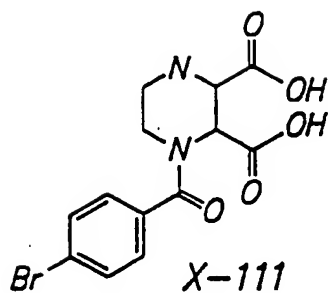
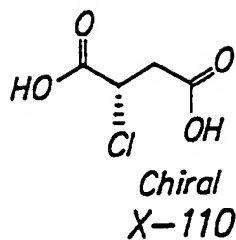
-67 (b)-



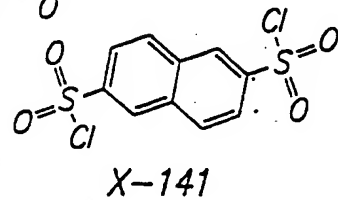
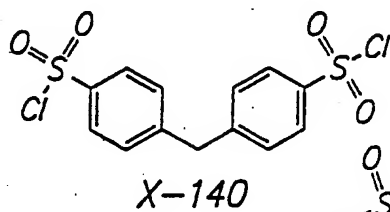
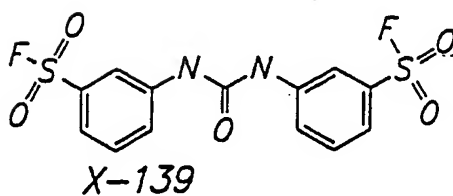
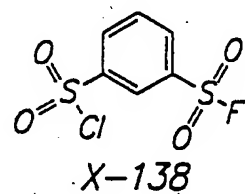
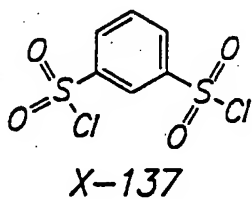
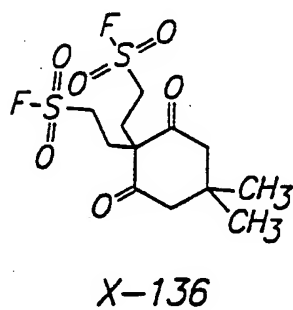
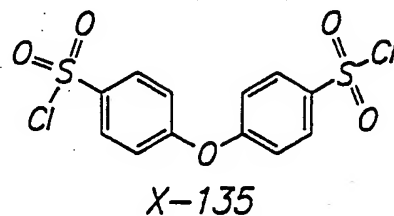
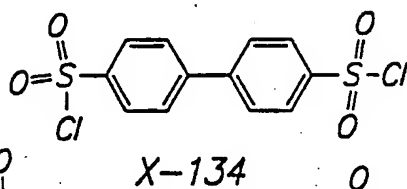
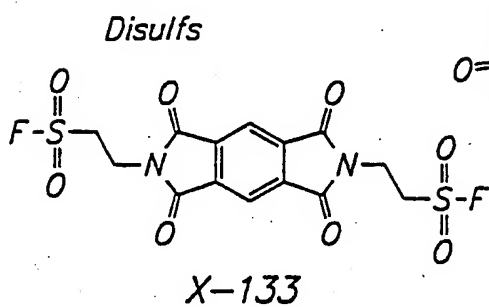
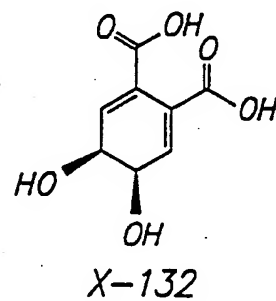
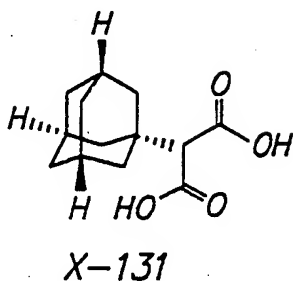
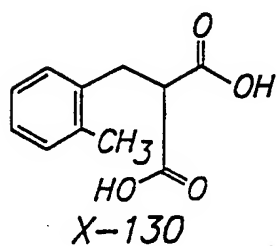
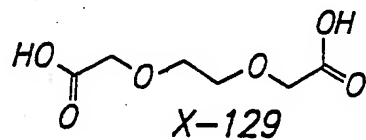
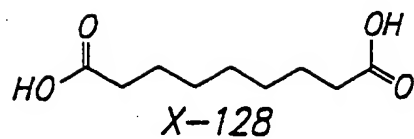
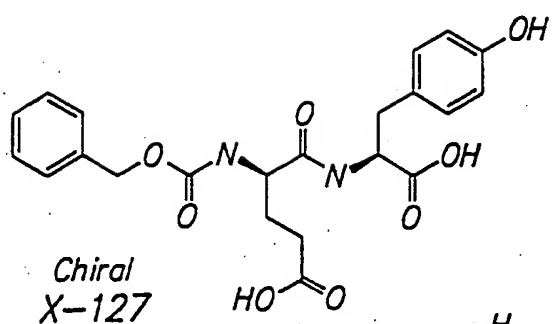
--67 (c)--



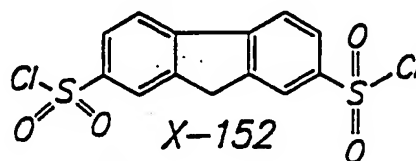
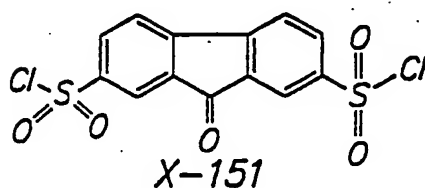
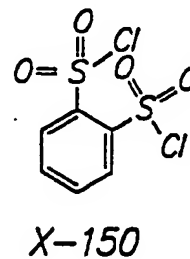
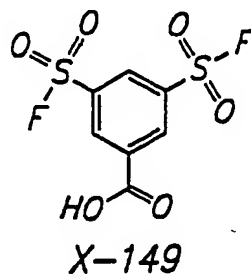
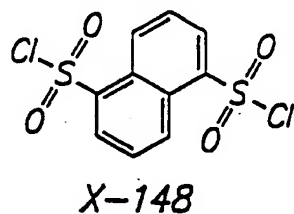
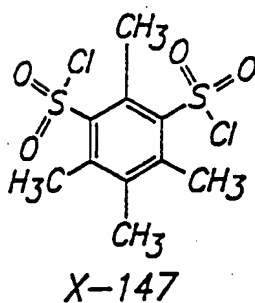
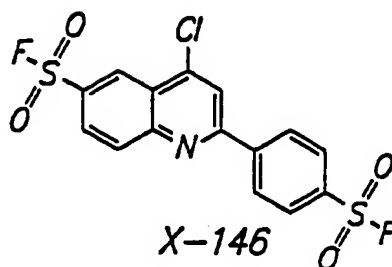
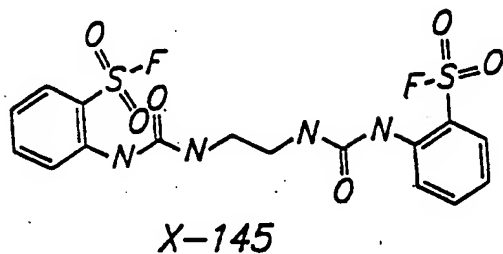
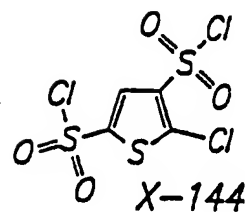
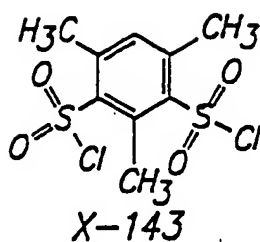
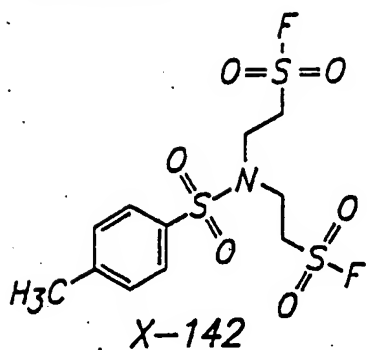
-67 (d)-



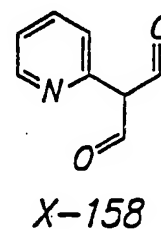
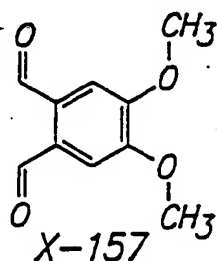
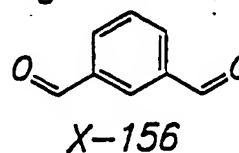
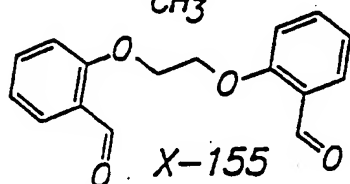
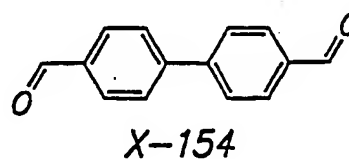
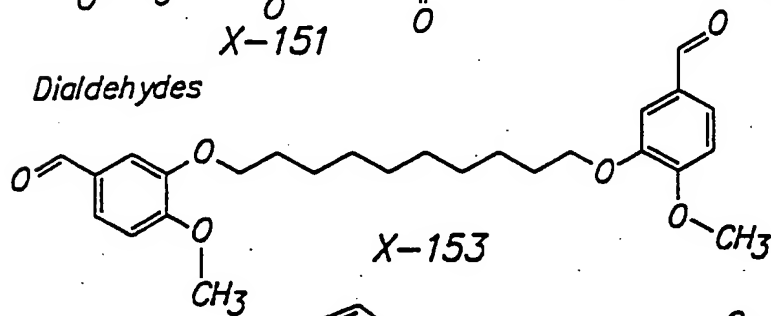
-67 (e)-



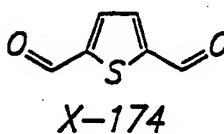
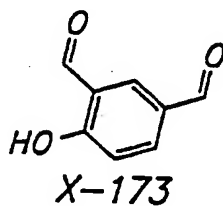
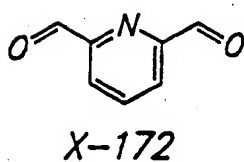
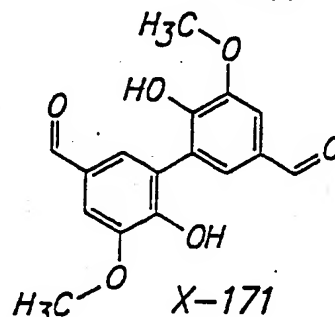
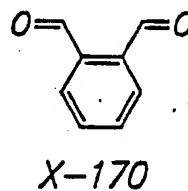
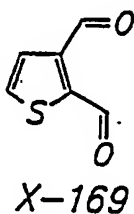
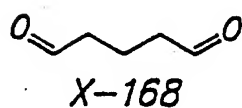
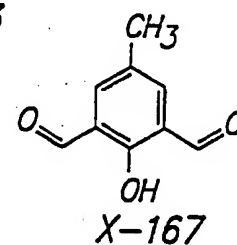
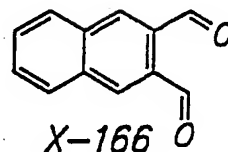
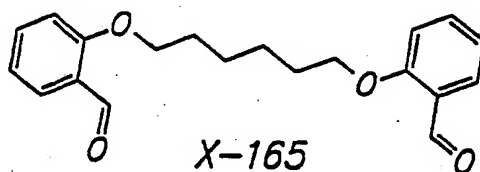
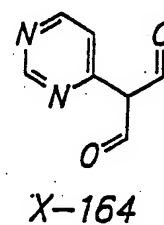
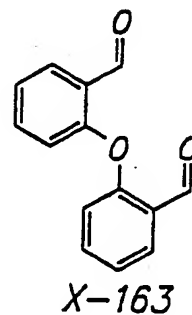
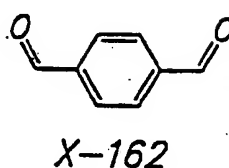
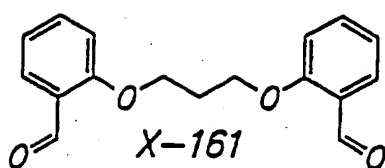
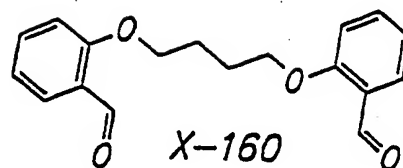
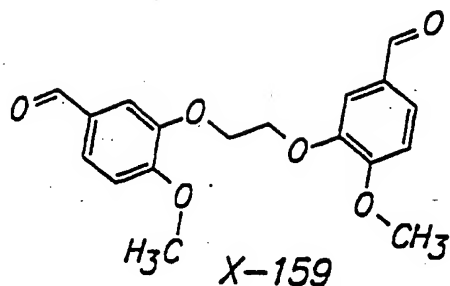
-67 (f)-



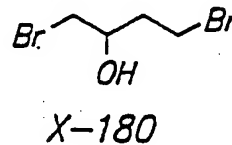
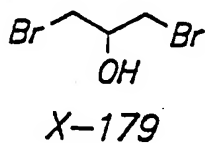
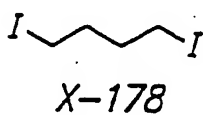
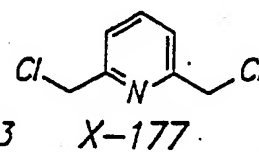
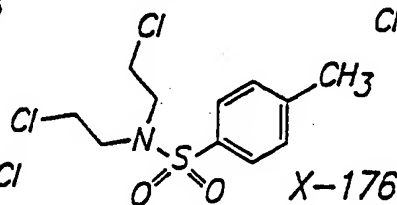
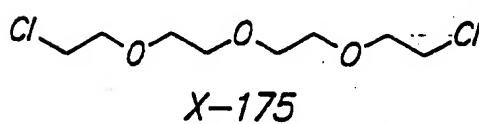
Dialdehydes

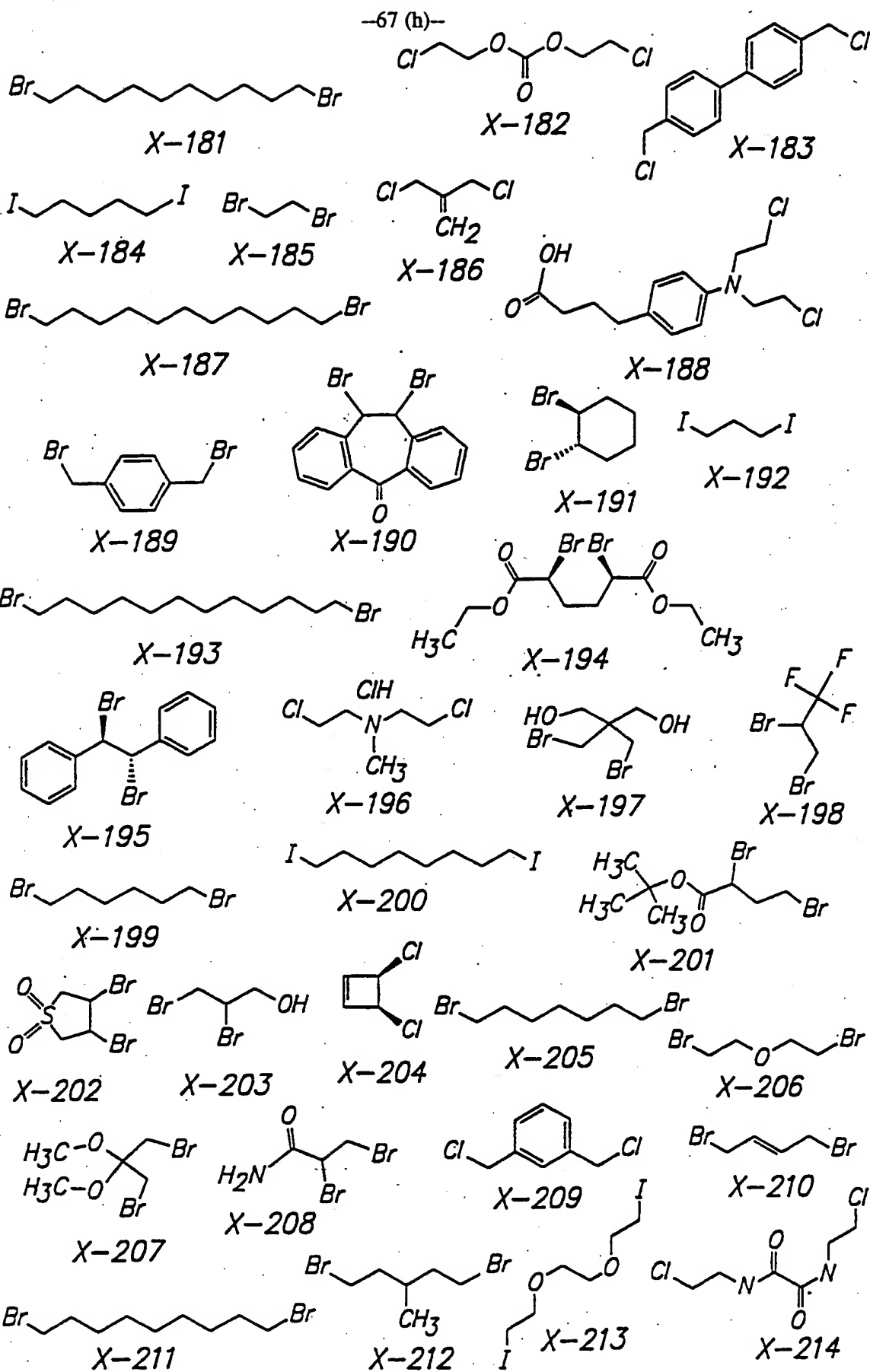


-67 (g)-



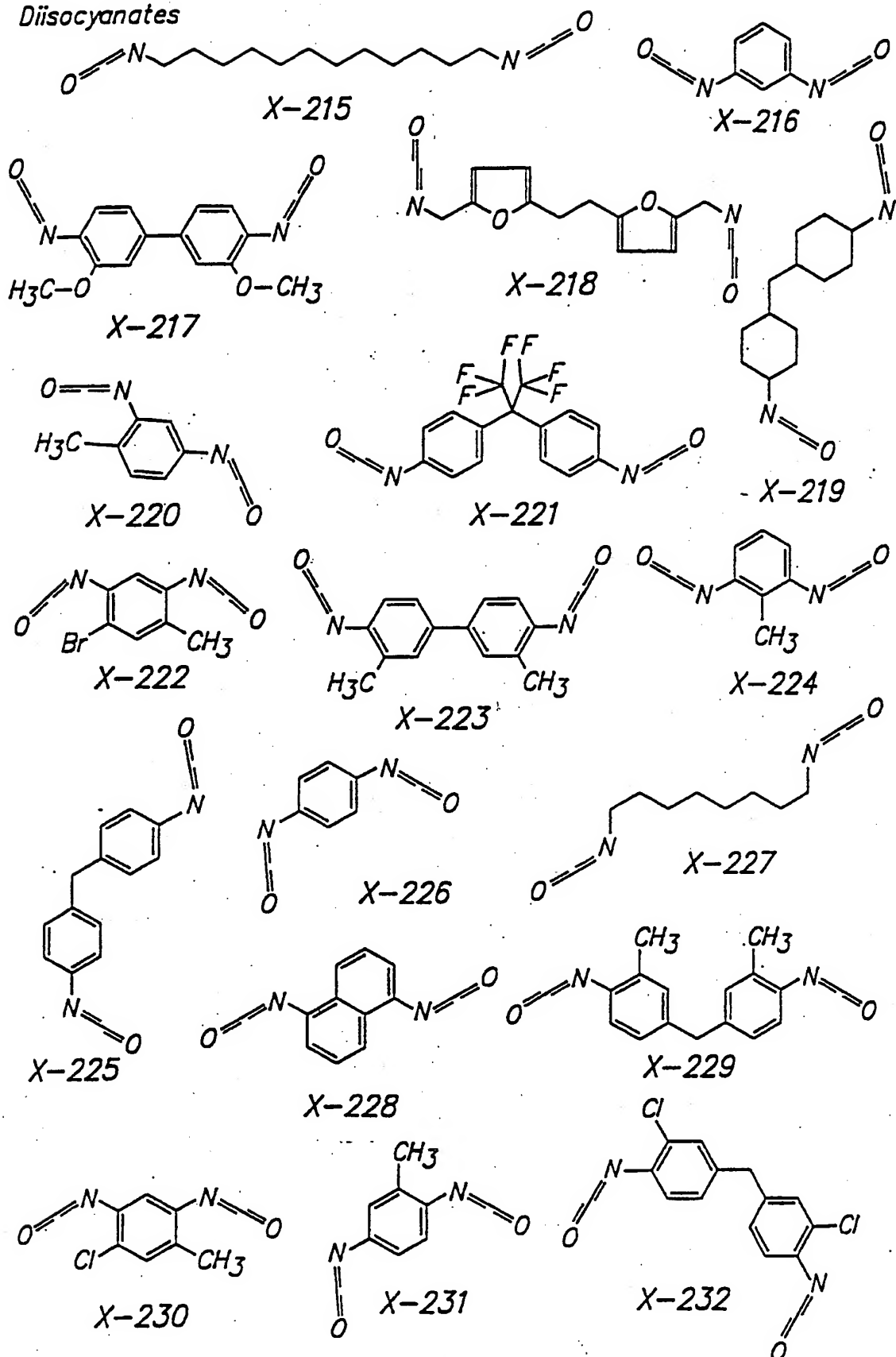
Dihalides





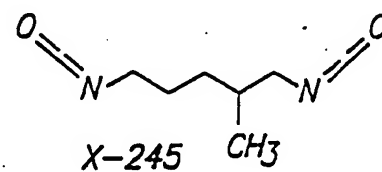
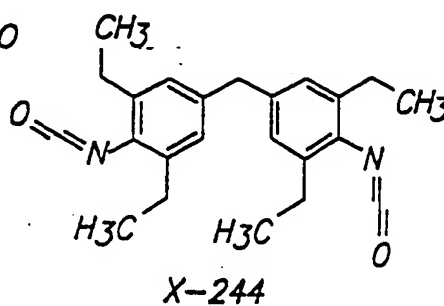
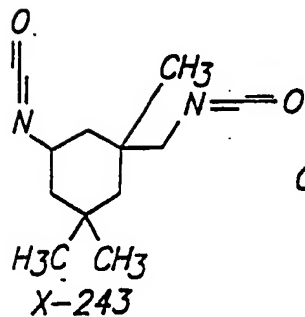
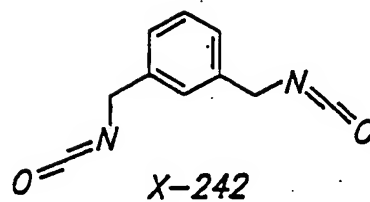
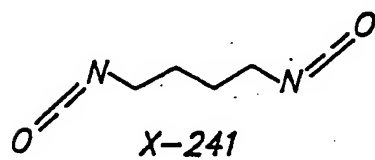
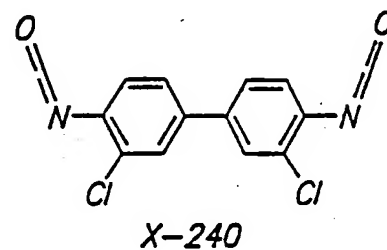
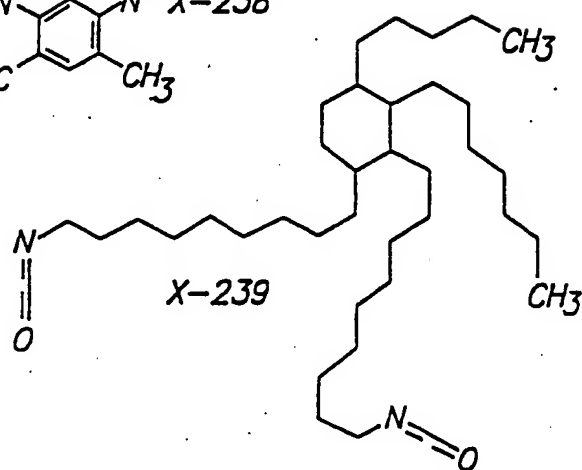
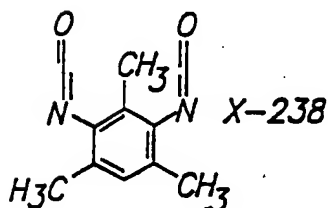
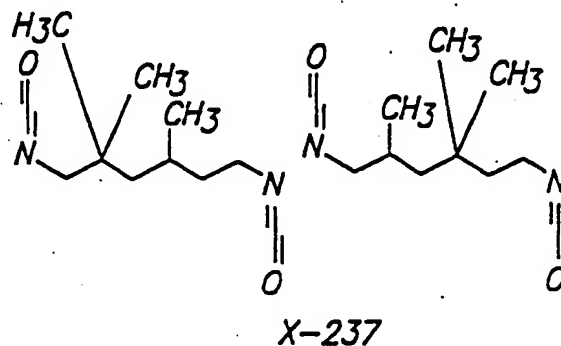
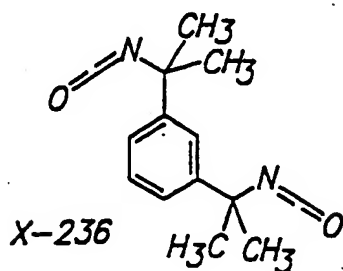
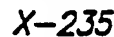
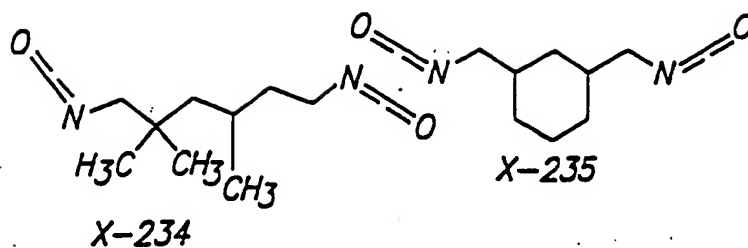
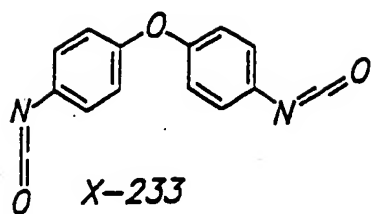
-67 (i)-

## Diisocyanates

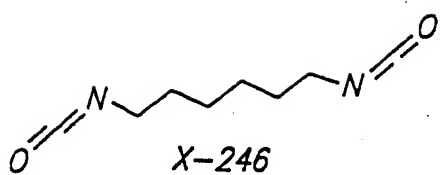




--67 (j)--

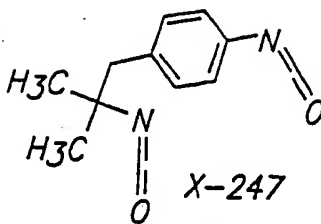


-67 (k)-

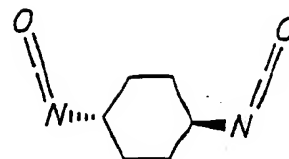


X-246

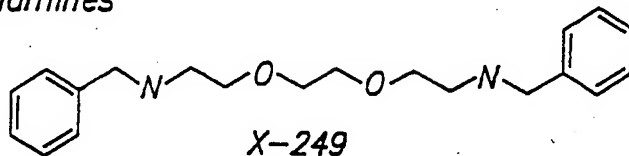
Diamines



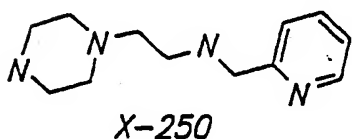
X-247



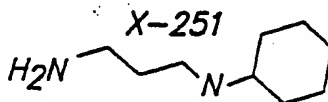
X-248



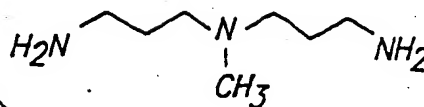
X-249



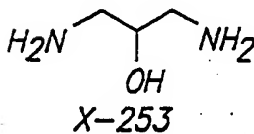
X-250



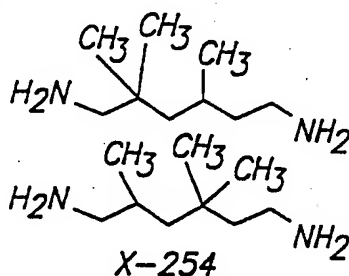
X-251



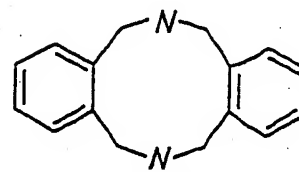
X-252



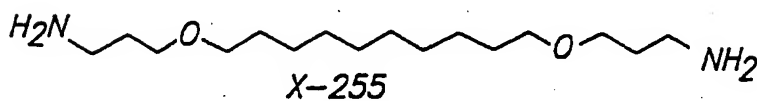
X-253



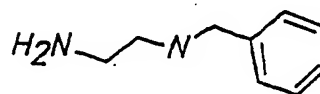
X-254



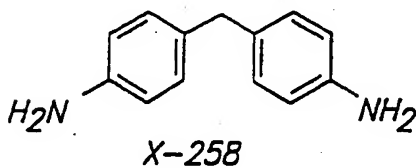
X-256



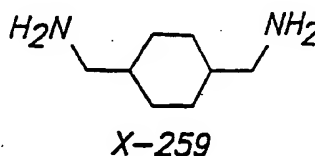
X-255



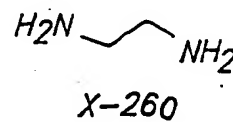
X-257



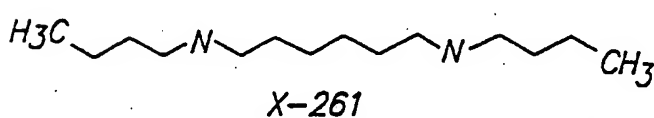
X-258



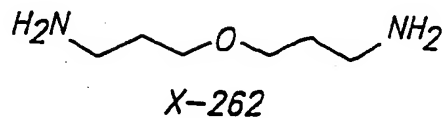
X-259



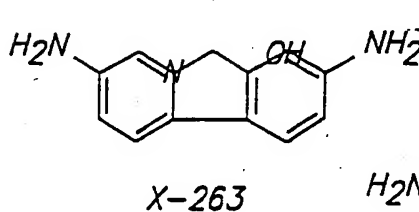
X-260



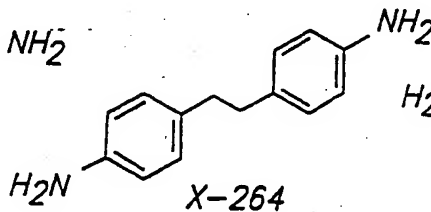
X-261



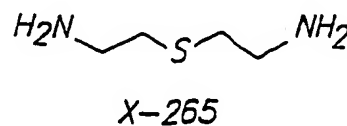
X-262



X-263

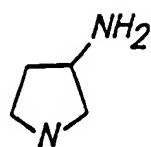


X-264

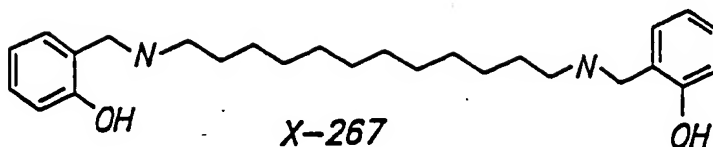


X-265

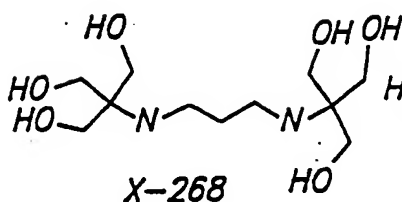
--67 (I)--



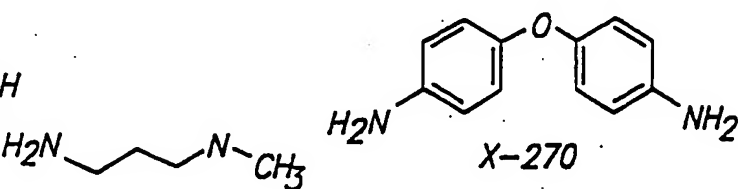
X-266



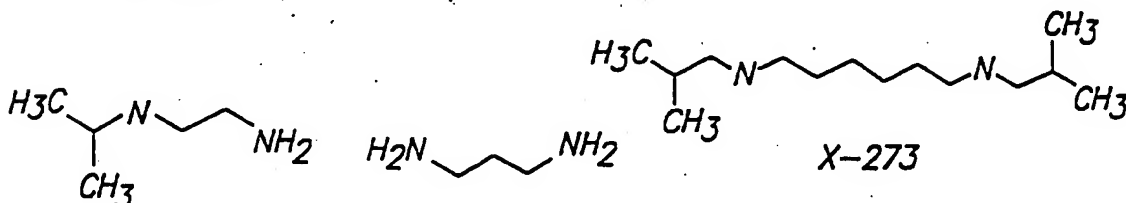
X-267



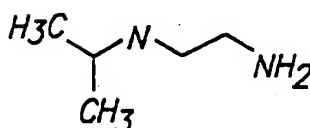
X-268



X-269



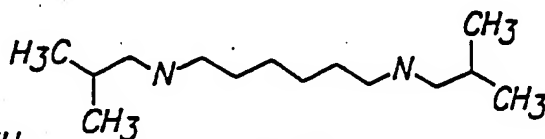
X-270



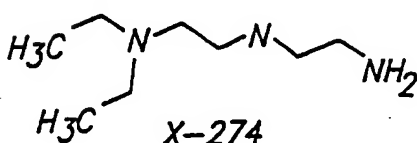
X-271



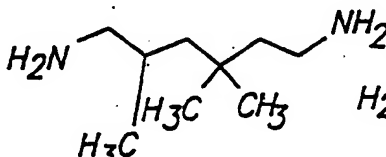
X-272



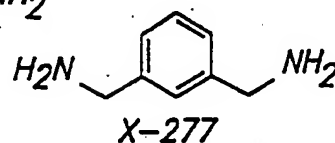
X-273



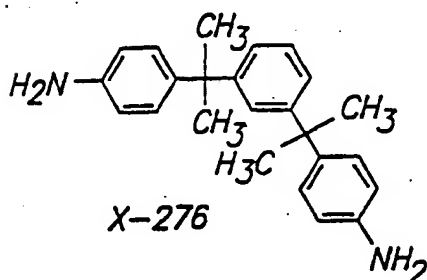
X-274



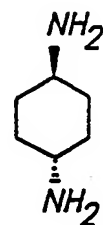
X-275



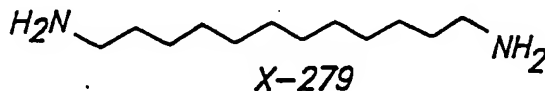
X-276



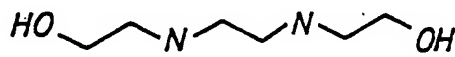
X-277



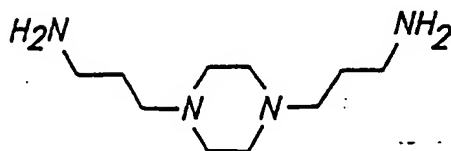
X-278



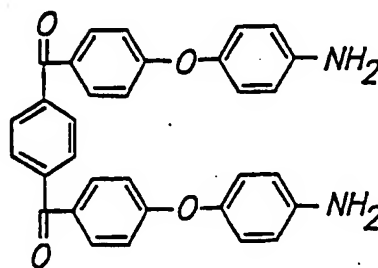
X-279



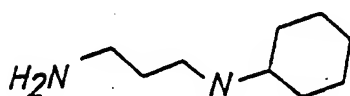
X-280



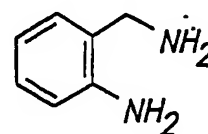
X-281



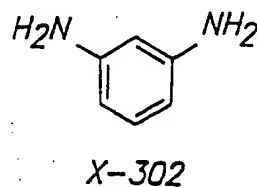
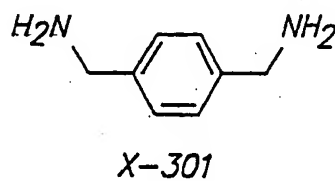
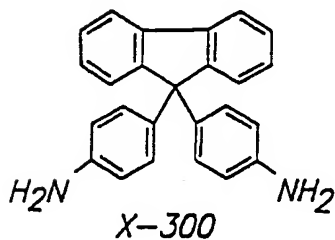
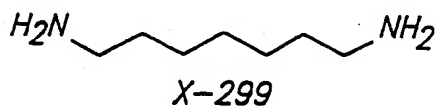
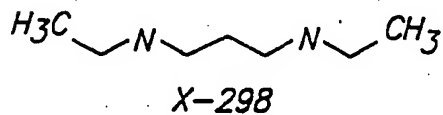
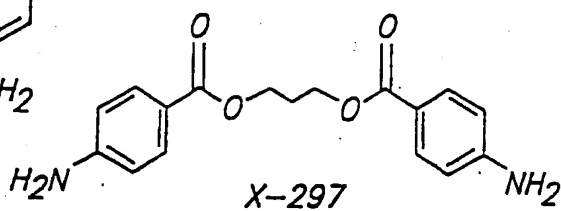
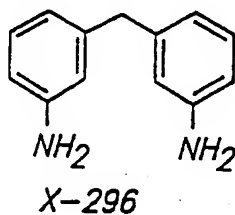
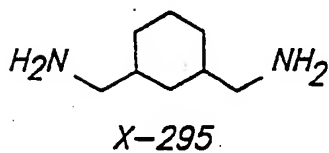
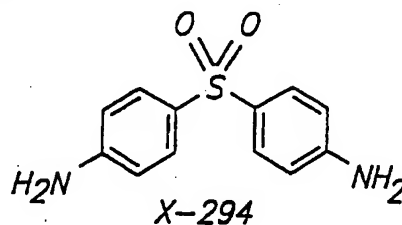
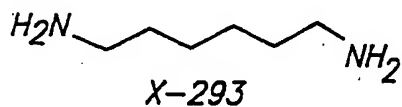
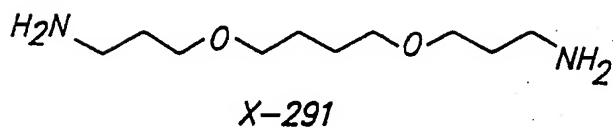
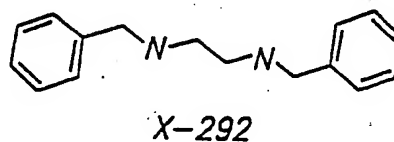
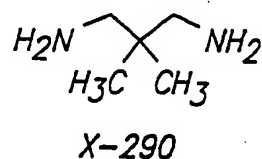
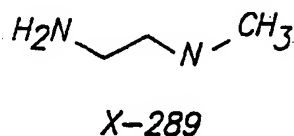
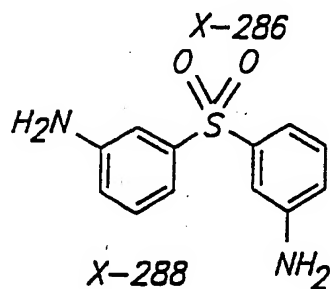
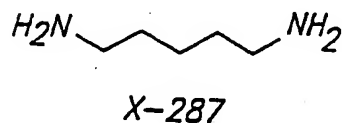
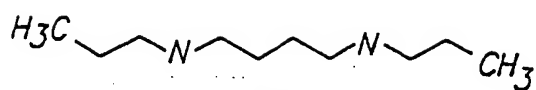
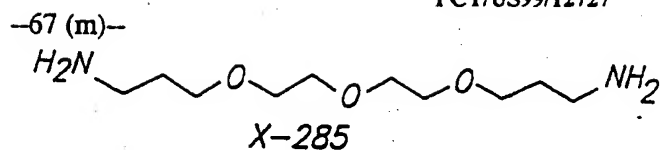
X-282

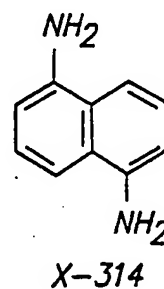
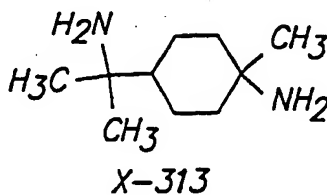
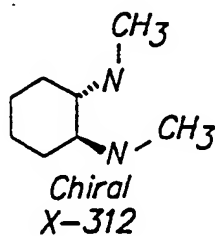
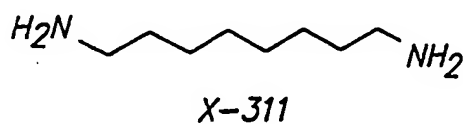
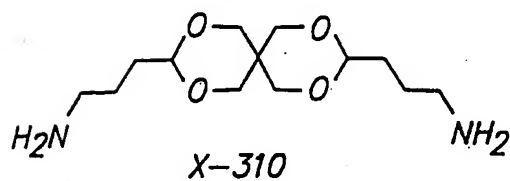
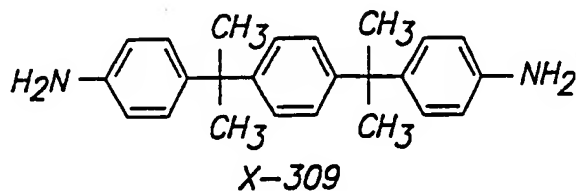
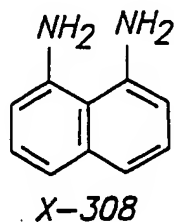
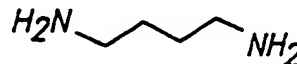
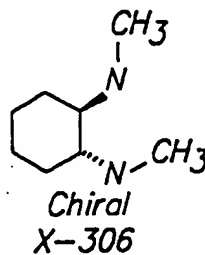
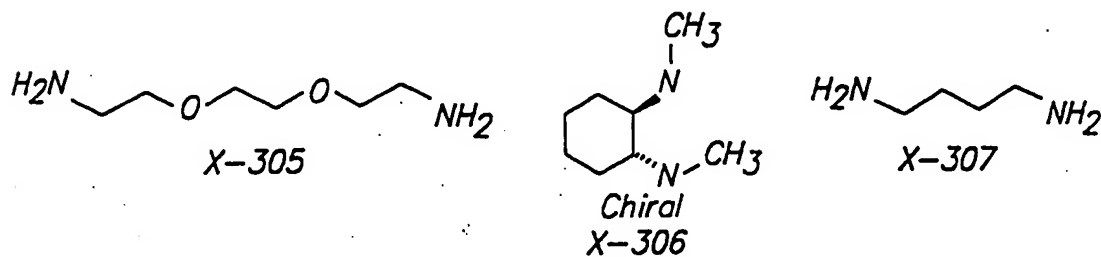
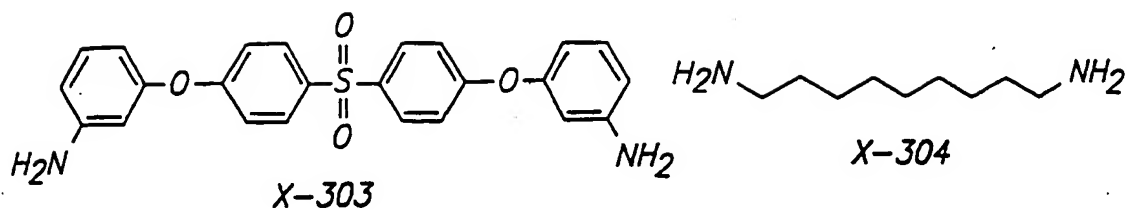


X-283

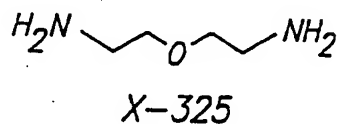
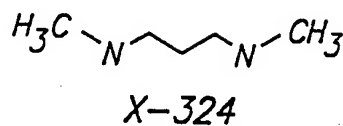
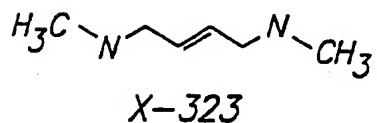
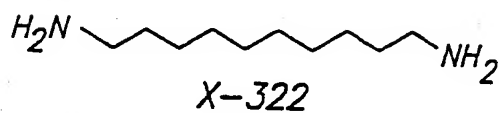
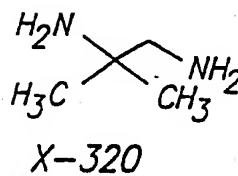
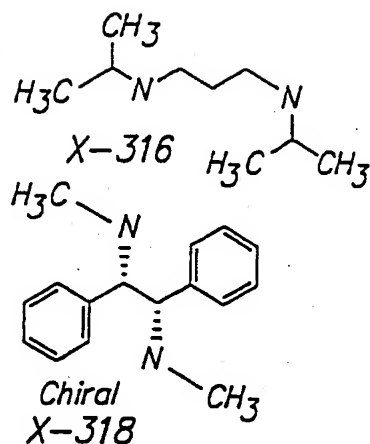
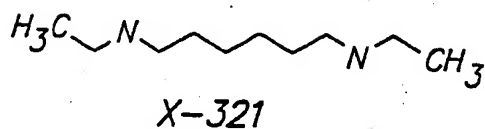
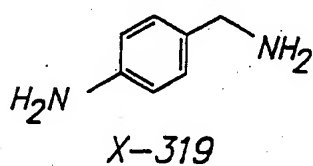
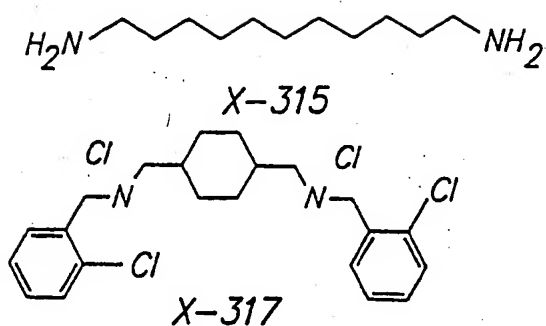


SUBSTITUTE SHEET (RULE 26)

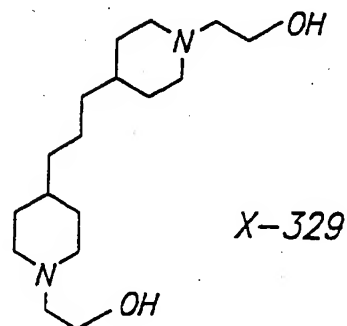
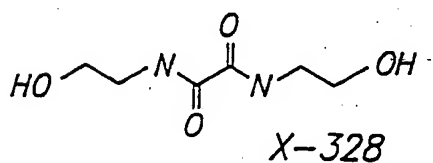
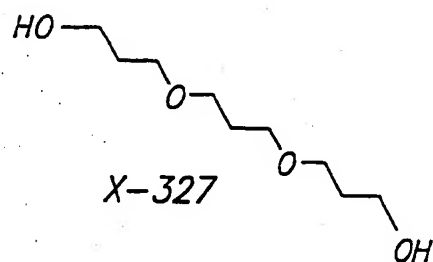
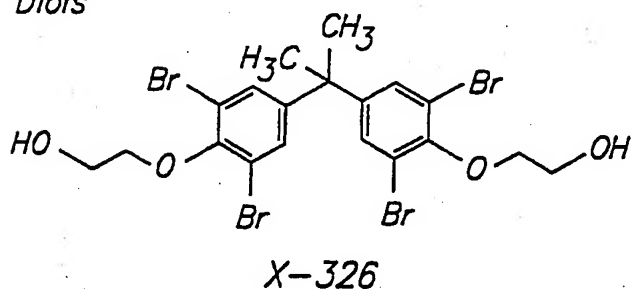




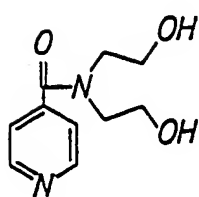
--67 (o)--



## Diols



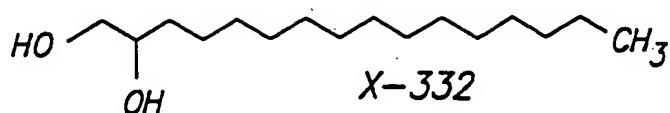
-67 (p)-



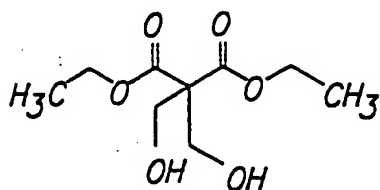
X-330



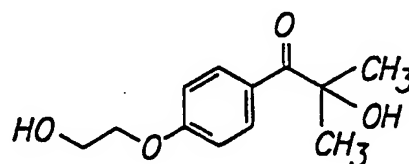
X-331



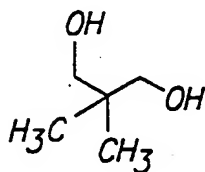
X-332



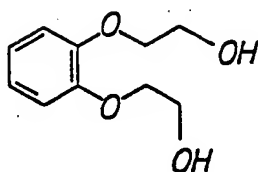
X-333



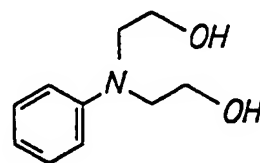
X-334



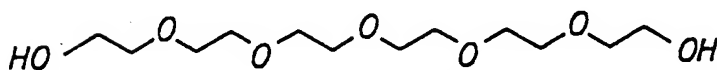
X-335



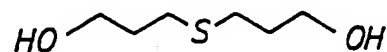
X-336



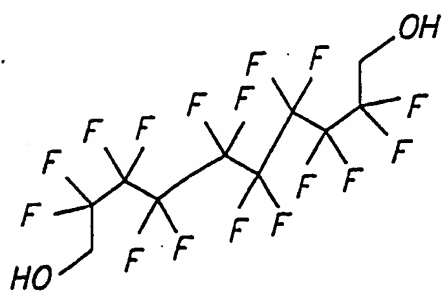
X-337



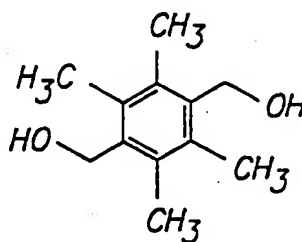
X-338



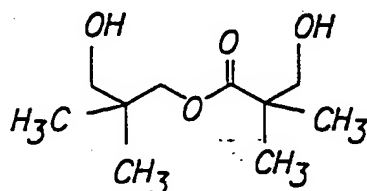
X-339



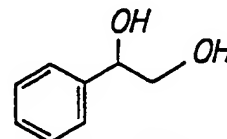
X-340



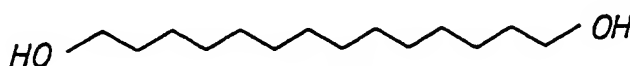
X-341



X-342

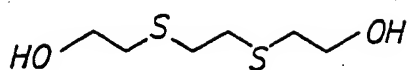


X-343

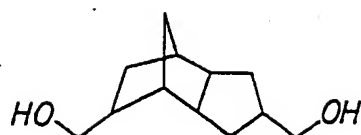


X-344

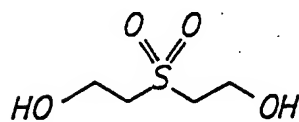
--67 (q)--



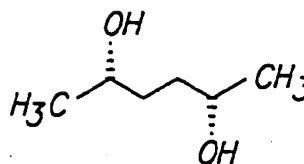
X-345



X-346



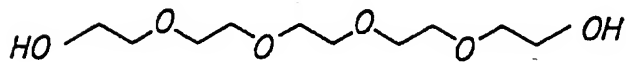
X-347



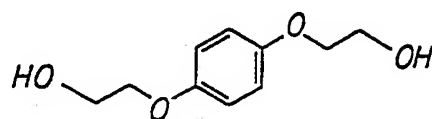
X-348



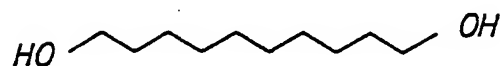
X-349



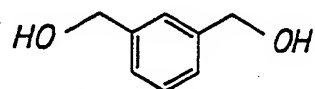
X-350



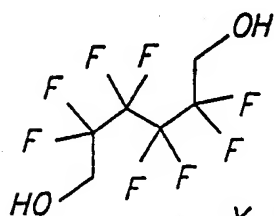
X-351



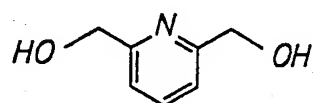
X-352



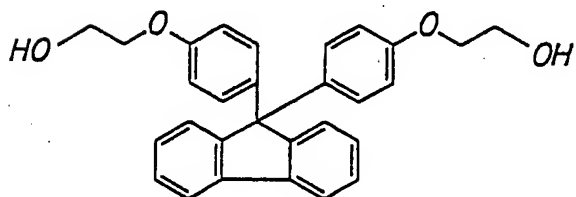
X-353



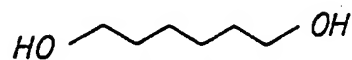
X-354



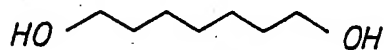
X-355



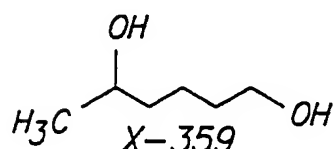
X-356



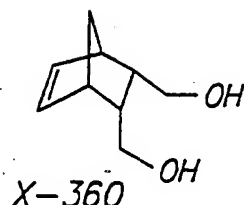
X-357



X-358

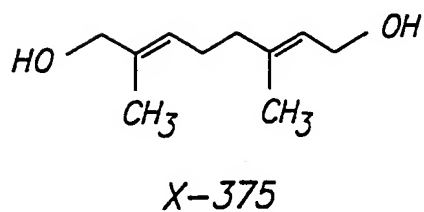
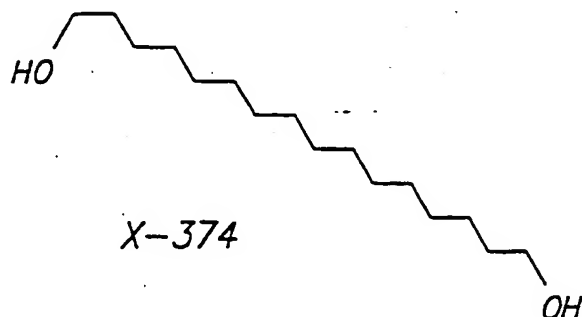
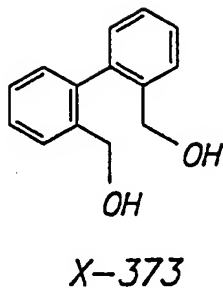
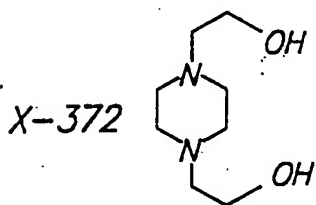
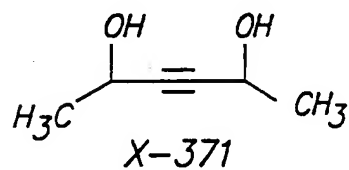
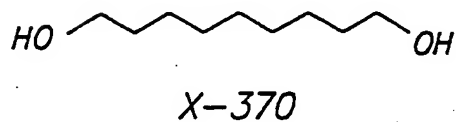
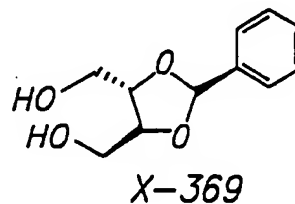
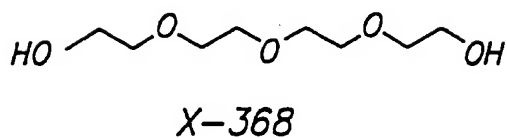
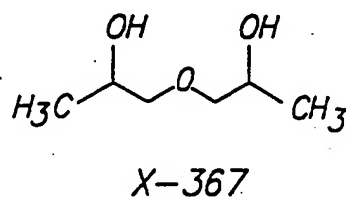
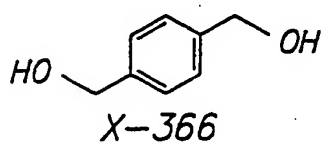
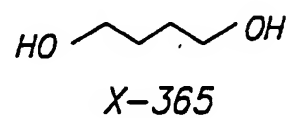
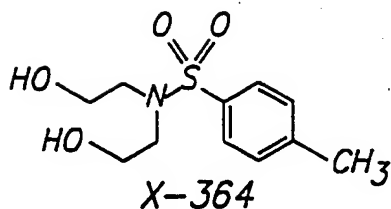
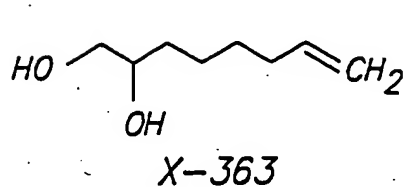
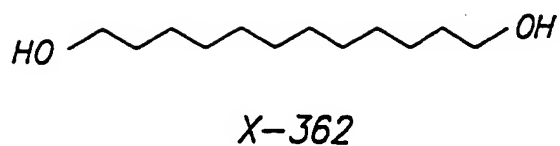
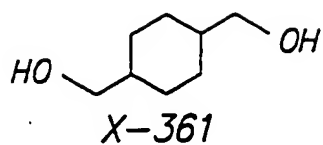


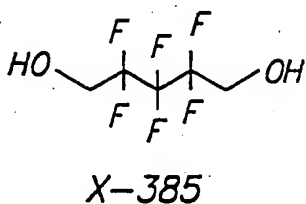
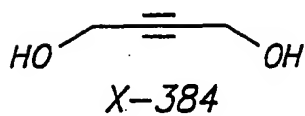
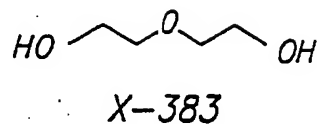
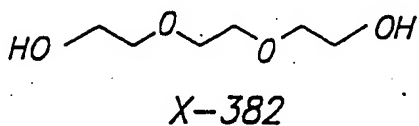
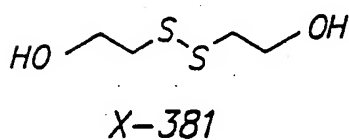
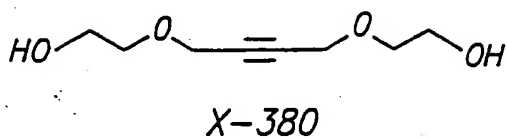
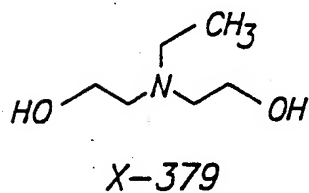
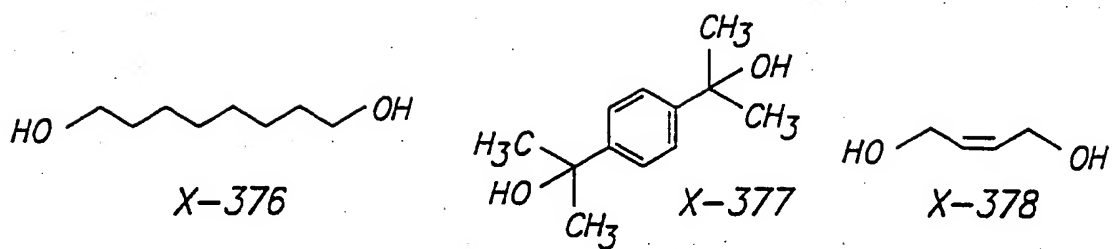
X-359



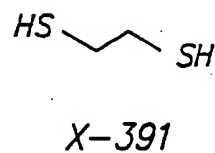
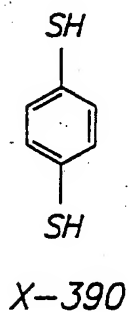
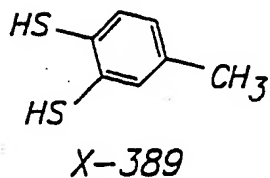
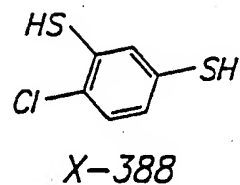
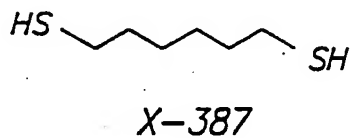
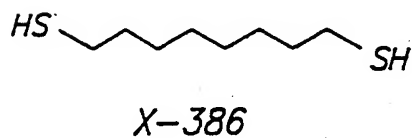
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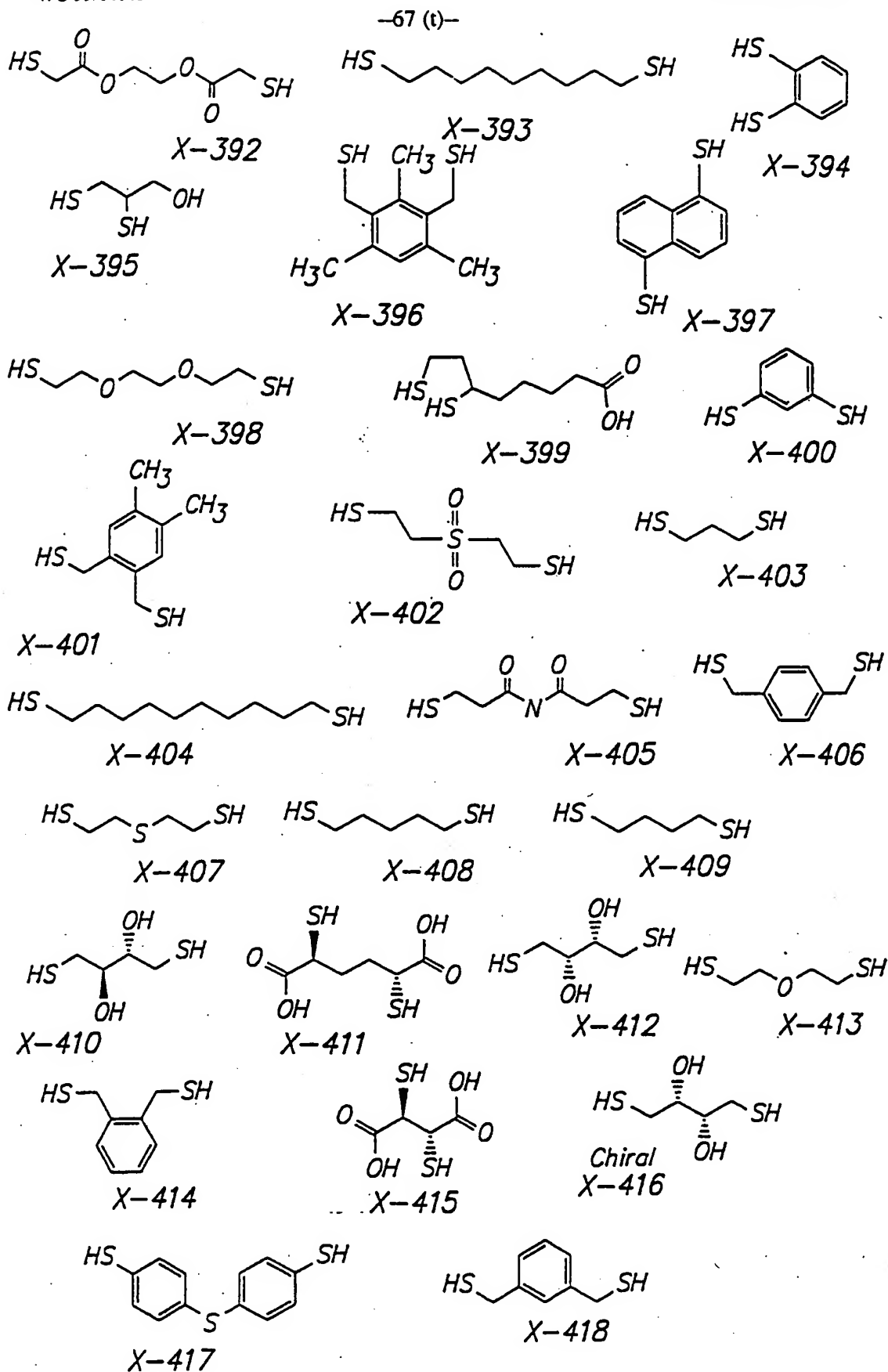






### Dithiols





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Representative ligands for use in this invention include, by way of example, L-1 through L-7 as identified above.

Combinations of ligands (L) and linkers (X) per this invention include, by way example only, homo- and hetero-dimers wherein a first ligand is selected from L-1 through L-7 above and the second ligand and linker is selected from the following:

	L-1/X-1-	L-1/X-2-	L-1/X-3-	L-1/X-4-	L-1/X-5-	L-1/X-6-
	L-1/X-7-	L-1/X-8-	L-1/X-9-	L-1/X-10-	L-1/X-11-	L-1/X-12-
	L-1/X-13-	L-1/X-14-	L-1/X-15-	L-1/X-16-	L-1/X-17-	L-1/X-18-
10	L-1/X-19-	L-1/X-20-	L-1/X-21-	L-1/X-22-	L-1/X-23-	L-1/X-24-
	L-1/X-25-	L-1/X-26-	L-1/X-27-	L-1/X-28-	L-1/X-29-	L-1/X-30-
	L-1/X-31-	L-1/X-32-	L-1/X-33-	L-1/X-34-	L-1/X-35-	L-1/X-36-
	L-1/X-37-	L-1/X-38-	L-1/X-39-	L-1/X-40-	L-1/X-41-	L-1/X-42-
	L-1/X-43-	L-1/X-44-	L-1/X-45-	L-1/X-46-	L-1/X-47-	L-1/X-48-
15	L-1/X-49-	L-1/X-50-	L-1/X-51-	L-1/X-52-	L-1/X-53-	L-1/X-54-
	L-1/X-55-	L-1/X-56-	L-1/X-57-	L-1/X-58-	L-1/X-59-	L-1/X-60-
	L-1/X-61-	L-1/X-62-	L-1/X-63-	L-1/X-64-	L-1/X-65-	L-1/X-66-
	L-1/X-67-	L-1/X-68-	L-1/X-69-	L-1/X-70-	L-1/X-71-	L-1/X-72-
	L-1/X-73-	L-1/X-74-	L-1/X-75-	L-1/X-76-	L-1/X-77-	L-1/X-78-
20	L-1/X-79-	L-1/X-80-	L-1/X-81-	L-1/X-82-	L-1/X-83-	L-1/X-84-
	L-1/X-85-	L-1/X-86-	L-1/X-87-	L-1/X-88-	L-1/X-89-	L-1/X-90-
	L-1/X-91-	L-1/X-92-	L-1/X-93-	L-1/X-94-	L-1/X-95-	L-1/X-96-
	L-1/X-97-	L-1/X-98-	L-1/X-99-	L-1/X-100-	L-1/X-101-	L-1/X-102-
	L-1/X-103-	L-1/X-104-	L-1/X-105-	L-1/X-106-	L-1/X-107-	L-1/X-108-
25	L-1/X-109-	L-1/X-110-	L-1/X-111-	L-1/X-112-	L-1/X-113-	L-1/X-114-
	L-1/X-115-	L-1/X-116-	L-1/X-117-	L-1/X-118-	L-1/X-119-	L-1/X-120-
	L-1/X-121-	L-1/X-122-	L-1/X-123-	L-1/X-124-	L-1/X-125-	L-1/X-126-
	L-1/X-127-	L-1/X-128-	L-1/X-129-	L-1/X-130-	L-1/X-131-	L-1/X-132-
	L-1/X-133-	L-1/X-134-	L-1/X-135-	L-1/X-136-	L-1/X-137-	L-1/X-138-
30	L-1/X-139-	L-1/X-140-	L-1/X-141-	L-1/X-142-	L-1/X-143-	L-1/X-144-
	L-1/X-145-	L-1/X-146-	L-1/X-147-	L-1/X-148-	L-1/X-149-	L-1/X-150-
	L-1/X-151-	L-1/X-152-	L-1/X-153-	L-1/X-154-	L-1/X-155-	L-1/X-156-
	L-1/X-157-	L-1/X-158-	L-1/X-159-	L-1/X-160-	L-1/X-161-	L-1/X-162-
	L-1/X-163-	L-1/X-164-	L-1/X-165-	L-1/X-166-	L-1/X-167-	L-1/X-168-
35	L-1/X-169-	L-1/X-170-	L-1/X-171-	L-1/X-172-		
	L-1/X-173-	L-1/X-174-	L-1/X-175-	L-1/X-176-	L-1/X-177-	L-1/X-178-
	L-1/X-179-	L-1/X-180-	L-1/X-181-	L-1/X-182-	L-1/X-183-	L-1/X-184-
	L-1/X-185-	L-1/X-186-	L-1/X-187-	L-1/X-188-	L-1/X-189-	L-1/X-190-
	L-1/X-191-	L-1/X-192-	L-1/X-193-	L-1/X-194-	L-1/X-195-	L-1/X-196-
40	L-1/X-197-	L-1/X-198-	L-1/X-199-	L-1/X-200-	L-1/X-201-	L-1/X-202-
	L-1/X-203-	L-1/X-204-	L-1/X-205-	L-1/X-206-	L-1/X-207-	L-1/X-208-
	L-1/X-209-	L-1/X-210-	L-1/X-211-	L-1/X-212-	L-1/X-213-	L-1/X-214-
	L-1/X-215-	L-1/X-216-	L-1/X-217-	L-1/X-218-	L-1/X-219-	L-1/X-220-

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	L-1/X-221-	L-1/X-222-	L-1/X-223-	L-1/X-224-	L-1/X-225-	L-1/X-226-
	L-1/X-227-	L-1/X-228-	L-1/X-229-	L-1/X-230-	L-1/X-231-	L-1/X-232-
	L-1/X-233-	L-1/X-234-	L-1/X-235-	L-1/X-236-	L-1/X-237-	L-1/X-238-
	L-1/X-239-	L-1/X-240-	L-1/X-241-	L-1/X-242-	L-1/X-243-	L-1/X-244-
5	L-1/X-245-	L-1/X-246-	L-1/X-247-	L-1/X-248-	L-1/X-249-	L-1/X-250-
	L-1/X-251-	L-1/X-252-	L-1/X-253-	L-1/X-254-	L-1/X-255-	L-1/X-256-
	L-1/X-257-	L-1/X-258-	L-1/X-259-	L-1/X-260-	L-1/X-261-	L-1/X-262-
	L-1/X-263-	L-1/X-264-	L-1/X-265-	L-1/X-266-	L-1/X-267-	L-1/X-268-
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	L-1/X-287-	L-1/X-288-	L-1/X-289-	L-1/X-290-	L-1/X-291-	L-1/X-292-
	L-1/X-293-	L-1/X-294-	L-1/X-295-	L-1/X-296-	L-1/X-297-	L-1/X-298-
	L-1/X-299-	L-1/X-300-	L-1/X-301-	L-1/X-302-	L-1/X-303-	L-1/X-304-
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	L-1/X-317-	L-1/X-318-	L-1/X-319-	L-1/X-320-	L-1/X-321-	L-1/X-322-
	L-1/X-323-	L-1/X-324-	L-1/X-325-	L-1/X-326-	L-1/X-327-	L-1/X-328-
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	L-1/X-341-	L-1/X-342-	L-1/X-343-	L-1/X-344-	L-1/X-345-	L-1/X-346-
	L-1/X-347-	L-1/X-348-	L-1/X-349-	L-1/X-350-	L-1/X-351-	L-1/X-352-
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	L-1/X-359-	L-1/X-360-	L-1/X-361-	L-1/X-362-	L-1/X-363-	L-1/X-364-
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	L-1/X-383-	L-1/X-384-	L-1/X-385-	L-1/X-386-	L-1/X-387-	L-1/X-388-
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	L-1/X-407-	L-1/X-408-	L-1/X-409-	L-1/X-410-	L-1/X-411-	L-1/X-412-
	L-1/X-413-	L-1/X-414-	L-1/X-415-	L-1/X-416-	L-1/X-417-	L-1/X-418-
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	L-2/X-25-	L-2/X-26-	L-2/X-27-	L-2/X-28-	L-2/X-29-	L-2/X-30-
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	L-2/X-133-	L-2/X-134-	L-2/X-135-	L-2/X-136-	L-2/X-137-	L-2/X-138-
	L-2/X-139-	L-2/X-140-	L-2/X-141-	L-2/X-142-	L-2/X-143-	L-2/X-144-
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	L-2/X-157-	L-2/X-158-	L-2/X-159-	L-2/X-160-	L-2/X-161-	L-2/X-162-
	L-2/X-163-	L-2/X-164-	L-2/X-165-	L-2/X-166-	L-2/X-167-	L-2/X-168-
	L-2/X-169-	L-2/X-170-	L-2/X-171-	L-2/X-172-		
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	L-2/X-215-	L-2/X-216-	L-2/X-217-	L-2/X-218-	L-2/X-219-	L-2/X-220-
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	L-2/X-245-	L-2/X-246-	L-2/X-247-	L-2/X-248-	L-2/X-249-	L-2/X-250-
	L-2/X-251-	L-2/X-252-	L-2/X-253-	L-2/X-254-	L-2/X-255-	L-2/X-256-
	L-2/X-257-	L-2/X-258-	L-2/X-259-	L-2/X-260-	L-2/X-261-	L-2/X-262-
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	L-2/X-287-	L-2/X-288-	L-2/X-289-	L-2/X-290-	L-2/X-291-	L-2/X-292-
	L-2/X-293-	L-2/X-294-	L-2/X-295-	L-2/X-296-	L-2/X-297-	L-2/X-298-
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	L-2/X-335-	L-2/X-336-	L-2/X-337-	L-2/X-338-	L-2/X-339-	L-2/X-340-
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	L-2/X-347-	L-2/X-348-	L-2/X-349-	L-2/X-350-	L-2/X-351-	L-2/X-352-
	L-2/X-353-	L-2/X-354-	L-2/X-355-	L-2/X-356-	L-2/X-357-	L-2/X-358-
45	L-2/X-359-	L-2/X-360-	L-2/X-361-	L-2/X-362-	L-2/X-363-	L-2/X-364-
	L-2/X-365-	L-2/X-366-	L-2/X-367-	L-2/X-368-	L-2/X-369-	L-2/X-370-
	L-2/X-371-	L-2/X-372-	L-2/X-373-	L-2/X-374-	L-2/X-375-	L-2/X-376-
	L-2/X-377-	L-2/X-378-	L-2/X-379-	L-2/X-380-	L-2/X-381-	L-2/X-382-
	L-2/X-383-	L-2/X-384-	L-2/X-385-	L-2/X-386-	L-2/X-387-	L-2/X-388-
	L-2/X-389-	L-2/X-390-	L-2/X-391-	L-2/X-392-	L-2/X-393-	L-2/X-394-
50	L-2/X-395-	L-2/X-396-	L-2/X-397-	L-2/X-398-	L-2/X-399-	L-2/X-400-
	L-2/X-401-	L-2/X-402-	L-2/X-403-	L-2/X-404-	L-2/X-405-	L-2/X-406-

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	L-2/X-407- L-2/X-413-	L-2/X-408- L-2/X-414-	L-2/X-409- L-2/X-415-	L-2/X-410- L-2/X-416-	L-2/X-411- L-2/X-417-	L-2/X-412- L-2/X-418-
	L-3/X-1- L-3/X-7-	L-3/X-2- L-3/X-8-	L-3/X-3- L-3/X-9-	L-3/X-4- L-3/X-10-	L-3/X-5- L-3/X-11-	L-3/X-6- L-3/X-12-
5	L-3/X-13- L-3/X-19- L-3/X-25- L-3/X-31-	L-3/X-14- L-3/X-20- L-3/X-26- L-3/X-32-	L-3/X-15- L-3/X-21- L-3/X-27- L-3/X-33-	L-3/X-16- L-3/X-22- L-3/X-28- L-3/X-34-	L-3/X-17- L-3/X-23- L-3/X-29- L-3/X-35-	L-3/X-18- L-3/X-24- L-3/X-30- L-3/X-36-
10	L-3/X-37- L-3/X-43- L-3/X-49- L-3/X-55- L-3/X-61- L-3/X-67-	L-3/X-38- L-3/X-44- L-3/X-50- L-3/X-56- L-3/X-62- L-3/X-68-	L-3/X-39- L-3/X-45- L-3/X-51- L-3/X-57- L-3/X-63- L-3/X-69-	L-3/X-40- L-3/X-46- L-3/X-52- L-3/X-58- L-3/X-64- L-3/X-70-	L-3/X-41- L-3/X-47- L-3/X-53- L-3/X-59- L-3/X-65- L-3/X-71-	L-3/X-42- L-3/X-48- L-3/X-54- L-3/X-60- L-3/X-66- L-3/X-72-
15	L-3/X-73- L-3/X-79- L-3/X-85- L-3/X-91- L-3/X-97-	L-3/X-74- L-3/X-80- L-3/X-86- L-3/X-92- L-3/X-98-	L-3/X-75- L-3/X-81- L-3/X-87- L-3/X-93- L-3/X-99-	L-3/X-76- L-3/X-82- L-3/X-88- L-3/X-94- L-3/X-100-	L-3/X-77- L-3/X-83- L-3/X-89- L-3/X-95- L-3/X-101-	L-3/X-78- L-3/X-84- L-3/X-90- L-3/X-96- L-3/X-102-
20	L-3/X-103- L-3/X-109- L-3/X-115- L-3/X-121- L-3/X-127-	L-3/X-104- L-3/X-110- L-3/X-116- L-3/X-122- L-3/X-128-	L-3/X-105- L-3/X-111- L-3/X-117- L-3/X-123- L-3/X-129-	L-3/X-106- L-3/X-112- L-3/X-118- L-3/X-124- L-3/X-130-	L-3/X-107- L-3/X-113- L-3/X-119- L-3/X-125- L-3/X-131-	L-3/X-108- L-3/X-114- L-3/X-120- L-3/X-126- L-3/X-132-
25	L-3/X-133- L-3/X-139- L-3/X-145- L-3/X-151- L-3/X-157-	L-3/X-134- L-3/X-140- L-3/X-146- L-3/X-152- L-3/X-158-	L-3/X-135- L-3/X-141- L-3/X-147- L-3/X-153- L-3/X-159-	L-3/X-136- L-3/X-142- L-3/X-148- L-3/X-154- L-3/X-160-	L-3/X-137- L-3/X-143- L-3/X-149- L-3/X-155- L-3/X-161-	L-3/X-138- L-3/X-144- L-3/X-150- L-3/X-156- L-3/X-162-
30	L-3/X-163- L-3/X-169- L-3/X-173- L-3/X-179- L-3/X-185-	L-3/X-164- L-3/X-170- L-3/X-174- L-3/X-180- L-3/X-186-	L-3/X-165- L-3/X-171- L-3/X-175- L-3/X-181- L-3/X-187-	L-3/X-166- L-3/X-172- L-3/X-176- L-3/X-182- L-3/X-188-	L-3/X-167- L-3/X-177- L-3/X-183- L-3/X-189- L-3/X-195-	L-3/X-168- L-3/X-178- L-3/X-184- L-3/X-190- L-3/X-196-
35	L-3/X-191- L-3/X-197- L-3/X-203- L-3/X-209- L-3/X-215-	L-3/X-192- L-3/X-198- L-3/X-204- L-3/X-210- L-3/X-216-	L-3/X-193- L-3/X-199- L-3/X-205- L-3/X-211- L-3/X-217-	L-3/X-194- L-3/X-200- L-3/X-206- L-3/X-212- L-3/X-218-	L-3/X-195- L-3/X-201- L-3/X-207- L-3/X-213- L-3/X-219-	L-3/X-196- L-3/X-202- L-3/X-208- L-3/X-214- L-3/X-220-
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	L-3/X-281-	L-3/X-282-	L-3/X-283-	L-3/X-284-	L-3/X-285-	L-3/X-286-
	L-3/X-287-	L-3/X-288-	L-3/X-289-	L-3/X-290-	L-3/X-291-	L-3/X-292-
	L-3/X-293-	L-3/X-294-	L-3/X-295-	L-3/X-296-	L-3/X-297-	L-3/X-298-
	L-3/X-299-	L-3/X-300-	L-3/X-301-	L-3/X-302-	L-3/X-303-	L-3/X-304-
5	L-3/X-305-	L-3/X-306-	L-3/X-307-	L-3/X-308-	L-3/X-309-	L-3/X-310-
	L-3/X-311-	L-3/X-312-	L-3/X-313-	L-3/X-314-	L-3/X-315-	L-3/X-316-
	L-3/X-317-	L-3/X-318-	L-3/X-319-	L-3/X-320-	L-3/X-321-	L-3/X-322-
	L-3/X-323-	L-3/X-324-	L-3/X-325-	L-3/X-326-	L-3/X-327-	L-3/X-328-
	L-3/X-329-	L-3/X-330-	L-3/X-331-	L-3/X-332-	L-3/X-333-	L-3/X-334-
10	L-3/X-335-	L-3/X-336-	L-3/X-337-	L-3/X-338-	L-3/X-339-	L-3/X-340-
	L-3/X-341-	L-3/X-342-	L-3/X-343-	L-3/X-344-	L-3/X-345-	L-3/X-346-
	L-3/X-347-	L-3/X-348-	L-3/X-349-	L-3/X-350-	L-3/X-351-	L-3/X-352-
	L-3/X-353-	L-3/X-354-	L-3/X-355-	L-3/X-356-	L-3/X-357-	L-3/X-358-
	L-3/X-359-	L-3/X-360-	L-3/X-361-	L-3/X-362-	L-3/X-363-	L-3/X-364-
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	L-3/X-377-	L-3/X-378-	L-3/X-379-	L-3/X-380-	L-3/X-381-	L-3/X-382-
	L-3/X-383-	L-3/X-384-	L-3/X-385-	L-3/X-386-	L-3/X-387-	L-3/X-388-
	L-3/X-389-	L-3/X-390-	L-3/X-391-	L-3/X-392-	L-3/X-393-	L-3/X-394-
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	L-3/X-401-	L-3/X-402-	L-3/X-403-	L-3/X-404-	L-3/X-405-	L-3/X-406-
	L-3/X-407-	L-3/X-408-	L-3/X-409-	L-3/X-410-	L-3/X-411-	L-3/X-412-
	L-3/X-413-	L-3/X-414-	L-3/X-415-	L-3/X-416-	L-3/X-417-	L-3/X-418-
	L-4/X-1-	L-4/X-2-	L-4/X-3-	L-4/X-4-	L-4/X-5-	L-4/X-6-
25	L-4/X-7-	L-4/X-8-	L-4/X-9-	L-4/X-10-	L-4/X-11-	L-4/X-12-
	L-4/X-13-	L-4/X-14-	L-4/X-15-	L-4/X-16-	L-4/X-17-	L-4/X-18-
	L-4/X-19-	L-4/X-20-	L-4/X-21-	L-4/X-22-	L-4/X-23-	L-4/X-24-
	L-4/X-25-	L-4/X-26-	L-4/X-27-	L-4/X-28-	L-4/X-29-	L-4/X-30-
	L-4/X-31-	L-4/X-32-	L-4/X-33-	L-4/X-34-	L-4/X-35-	L-4/X-36-
30	L-4/X-37-	L-4/X-38-	L-4/X-39-	L-4/X-40-	L-4/X-41-	L-4/X-42-
	L-4/X-43-	L-4/X-44-	L-4/X-45-	L-4/X-46-	L-4/X-47-	L-4/X-48-
	L-4/X-49-	L-4/X-50-	L-4/X-51-	L-4/X-52-	L-4/X-53-	L-4/X-54-
	L-4/X-55-	L-4/X-56-	L-4/X-57-	L-4/X-58-	L-4/X-59-	L-4/X-60-
	L-4/X-61-	L-4/X-62-	L-4/X-63-	L-4/X-64-	L-4/X-65-	L-4/X-66-
35	L-4/X-67-	L-4/X-68-	L-4/X-69-	L-4/X-70-	L-4/X-71-	L-4/X-72-
	L-4/X-73-	L-4/X-74-	L-4/X-75-	L-4/X-76-	L-4/X-77-	L-4/X-78-
	L-4/X-79-	L-4/X-80-	L-4/X-81-	L-4/X-82-	L-4/X-83-	L-4/X-84-
	L-4/X-85-	L-4/X-86-	L-4/X-87-	L-4/X-88-	L-4/X-89-	L-4/X-90-
	L-4/X-91-	L-4/X-92-	L-4/X-93-	L-4/X-94-	L-4/X-95-	L-4/X-96-
40	L-4/X-97-	L-4/X-98-	L-4/X-99-	L-4/X-100-	L-4/X-101-	L-4/X-102-
	L-4/X-103-	L-4/X-104-	L-4/X-105-	L-4/X-106-	L-4/X-107-	L-4/X-108-
	L-4/X-109-	L-4/X-110-	L-4/X-111-	L-4/X-112-	L-4/X-113-	L-4/X-114-
	L-4/X-115-	L-4/X-116-	L-4/X-117-	L-4/X-118-	L-4/X-119-	L-4/X-120-
	L-4/X-121-	L-4/X-122-	L-4/X-123-	L-4/X-124-	L-4/X-125-	L-4/X-126-
45	L-4/X-127-	L-4/X-128-	L-4/X-129-	L-4/X-130-	L-4/X-131-	L-4/X-132-
	L-4/X-133-	L-4/X-134-	L-4/X-135-	L-4/X-136-	L-4/X-137-	L-4/X-138-
	L-4/X-139-	L-4/X-140-	L-4/X-141-	L-4/X-142-	L-4/X-143-	L-4/X-144-
	L-4/X-145-	L-4/X-146-	L-4/X-147-	L-4/X-148-	L-4/X-149-	L-4/X-150-
	L-4/X-151-	L-4/X-152-	L-4/X-153-	L-4/X-154-	L-4/X-155-	L-4/X-156-
50	L-4/X-157-	L-4/X-158-	L-4/X-159-	L-4/X-160-	L-4/X-161-	L-4/X-162-



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	L-4/X-163-	L-4/X-164-	L-4/X-165-	L-4/X-166-	L-4/X-167-	L-4/X-168-
	L-4/X-169-	L-4/X-170-	L-4/X-171-	L-4/X-172-		
	L-4/X-173-	L-4/X-174-	L-4/X-175-	L-4/X-176-	L-4/X-177-	L-4/X-178-
	L-4/X-179-	L-4/X-180-	L-4/X-181-	L-4/X-182-	L-4/X-183-	L-4/X-184-
5	L-4/X-185-	L-4/X-186-	L-4/X-187-	L-4/X-188-	L-4/X-189-	L-4/X-190-
	L-4/X-191-	L-4/X-192-	L-4/X-193-	L-4/X-194-	L-4/X-195-	L-4/X-196-
	L-4/X-197-	L-4/X-198-	L-4/X-199-	L-4/X-200-	L-4/X-201-	L-4/X-202-
	L-4/X-203-	L-4/X-204-	L-4/X-205-	L-4/X-206-	L-4/X-207-	L-4/X-208-
	L-4/X-209-	L-4/X-210-	L-4/X-211-	L-4/X-212-	L-4/X-213-	L-4/X-214-
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	L-4/X-221-	L-4/X-222-	L-4/X-223-	L-4/X-224-	L-4/X-225-	L-4/X-226-
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	L-4/X-233-	L-4/X-234-	L-4/X-235-	L-4/X-236-	L-4/X-237-	L-4/X-238-
	L-4/X-239-	L-4/X-240-	L-4/X-241-	L-4/X-242-	L-4/X-243-	L-4/X-244-
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	L-4/X-251-	L-4/X-252-	L-4/X-253-	L-4/X-254-	L-4/X-255-	L-4/X-256-
	L-4/X-257-	L-4/X-258-	L-4/X-259-	L-4/X-260-	L-4/X-261-	L-4/X-262-
	L-4/X-263-	L-4/X-264-	L-4/X-265-	L-4/X-266-	L-4/X-267-	L-4/X-268-
	L-4/X-269-	L-4/X-270-	L-4/X-271-	L-4/X-272-	L-4/X-273-	L-4/X-274-
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25	L-4/X-305-	L-4/X-306-	L-4/X-307-	L-4/X-308-	L-4/X-309-	L-4/X-310-
	L-4/X-311-	L-4/X-312-	L-4/X-313-	L-4/X-314-	L-4/X-315-	L-4/X-316-
	L-4/X-317-	L-4/X-318-	L-4/X-319-	L-4/X-320-	L-4/X-321-	L-4/X-322-
	L-4/X-323-	L-4/X-324-	L-4/X-325-	L-4/X-326-	L-4/X-327-	L-4/X-328-
	L-4/X-329-	L-4/X-330-	L-4/X-331-	L-4/X-332-	L-4/X-333-	L-4/X-334-
30	L-4/X-335-	L-4/X-336-	L-4/X-337-	L-4/X-338-	L-4/X-339-	L-4/X-340-
	L-4/X-341-	L-4/X-342-	L-4/X-343-	L-4/X-344-	L-4/X-345-	L-4/X-346-
	L-4/X-347-	L-4/X-348-	L-4/X-349-	L-4/X-350-	L-4/X-351-	L-4/X-352-
	L-4/X-353-	L-4/X-354-	L-4/X-355-	L-4/X-356-	L-4/X-357-	L-4/X-358-
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	L-4/X-371-	L-4/X-372-	L-4/X-373-	L-4/X-374-	L-4/X-375-	L-4/X-376-
	L-4/X-377-	L-4/X-378-	L-4/X-379-	L-4/X-380-	L-4/X-381-	L-4/X-382-
	L-4/X-383-	L-4/X-384-	L-4/X-385-	L-4/X-386-	L-4/X-387-	L-4/X-388-
	L-4/X-389-	L-4/X-390-	L-4/X-391-	L-4/X-392-	L-4/X-393-	L-4/X-394-
40	L-4/X-395-	L-4/X-396-	L-4/X-397-	L-4/X-398-	L-4/X-399-	L-4/X-400-
	L-4/X-401-	L-4/X-402-	L-4/X-403-	L-4/X-404-	L-4/X-405-	L-4/X-406-
	L-4/X-407-	L-4/X-408-	L-4/X-409-	L-4/X-410-	L-4/X-411-	L-4/X-412-
	L-4/X-413-	L-4/X-414-	L-4/X-415-	L-4/X-416-	L-4/X-417-	L-4/X-418-
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	L-5/X-31-	L-5/X-32-	L-5/X-33-	L-5/X-34-	L-5/X-35-	L-5/X-36-
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	L-5/X-353-	L-5/X-354-	L-5/X-355-	L-5/X-356-	L-5/X-357-	L-5/X-358-
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	L-6/X-389-	L-6/X-390-	L-6/X-391-	L-6/X-392-	L-6/X-393-	L-6/X-394-
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	L-7/X-7-	L-7/X-8-	L-7/X-9-	L-7/X-10-	L-7/X-11-	L-7/X-12-
	L-7/X-13-	L-7/X-14-	L-7/X-15-	L-7/X-16-	L-7/X-17-	L-7/X-18-
40	L-7/X-19-	L-7/X-20-	L-7/X-21-	L-7/X-22-	L-7/X-23-	L-7/X-24-
	L-7/X-25-	L-7/X-26-	L-7/X-27-	L-7/X-28-	L-7/X-29-	L-7/X-30-
	L-7/X-31-	L-7/X-32-	L-7/X-33-	L-7/X-34-	L-7/X-35-	L-7/X-36-
	L-7/X-37-	L-7/X-38-	L-7/X-39-	L-7/X-40-	L-7/X-41-	L-7/X-42-
	L-7/X-43-	L-7/X-44-	L-7/X-45-	L-7/X-46-	L-7/X-47-	L-7/X-48-
45	L-7/X-49-	L-7/X-50-	L-7/X-51-	L-7/X-52-	L-7/X-53-	L-7/X-54-
	L-7/X-55-	L-7/X-56-	L-7/X-57-	L-7/X-58-	L-7/X-59-	L-7/X-60-
	L-7/X-61-	L-7/X-62-	L-7/X-63-	L-7/X-64-	L-7/X-65-	L-7/X-66-
	L-7/X-67-	L-7/X-68-	L-7/X-69-	L-7/X-70-	L-7/X-71-	L-7/X-72-
	L-7/X-73-	L-7/X-74-	L-7/X-75-	L-7/X-76-	L-7/X-77-	L-7/X-78-
	L-7/X-79-	L-7/X-80-	L-7/X-81-	L-7/X-82-	L-7/X-83-	L-7/X-84-

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	L-7/X-85-	L-7/X-86-	L-7/X-87-	L-7/X-88-	L-7/X-89-	L-7/X-90-
	L-7/X-91-	L-7/X-92-	L-7/X-93-	L-7/X-94-	L-7/X-95-	L-7/X-96-
	L-7/X-97-	L-7/X-98-	L-7/X-99-	L-7/X-100-	L-7/X-101-	L-7/X-102-
	L-7/X-103-	L-7/X-104-	L-7/X-105-	L-7/X-106-	L-7/X-107-	L-7/X-108-
5	L-7/X-109-	L-7/X-110-	L-7/X-111-	L-7/X-112-	L-7/X-113-	L-7/X-114-
	L-7/X-115-	L-7/X-116-	L-7/X-117-	L-7/X-118-	L-7/X-119-	L-7/X-120-
	L-7/X-121-	L-7/X-122-	L-7/X-123-	L-7/X-124-	L-7/X-125-	L-7/X-126-
	L-7/X-127-	L-7/X-128-	L-7/X-129-	L-7/X-130-	L-7/X-131-	L-7/X-132-
	L-7/X-133-	L-7/X-134-	L-7/X-135-	L-7/X-136-	L-7/X-137-	L-7/X-138-
10	L-7/X-139-	L-7/X-140-	L-7/X-141-	L-7/X-142-	L-7/X-143-	L-7/X-144-
	L-7/X-145-	L-7/X-146-	L-7/X-147-	L-7/X-148-	L-7/X-149-	L-7/X-150-
	L-7/X-151-	L-7/X-152-	L-7/X-153-	L-7/X-154-	L-7/X-155-	L-7/X-156-
	L-7/X-157-	L-7/X-158-	L-7/X-159-	L-7/X-160-	L-7/X-161-	L-7/X-162-
	L-7/X-163-	L-7/X-164-	L-7/X-165-	L-7/X-166-	L-7/X-167-	L-7/X-168-
15	L-7/X-169-	L-7/X-170-	L-7/X-171-	L-7/X-172-		
	L-7/X-173-	L-7/X-174-	L-7/X-175-	L-7/X-176-	L-7/X-177-	L-7/X-178-
	L-7/X-179-	L-7/X-180-	L-7/X-181-	L-7/X-182-	L-7/X-183-	L-7/X-184-
	L-7/X-185-	L-7/X-186-	L-7/X-187-	L-7/X-188-	L-7/X-189-	L-7/X-190-
	L-7/X-191-	L-7/X-192-	L-7/X-193-	L-7/X-194-	L-7/X-195-	L-7/X-196-
20	L-7/X-197-	L-7/X-198-	L-7/X-199-	L-7/X-200-	L-7/X-201-	L-7/X-202-
	L-7/X-203-	L-7/X-204-	L-7/X-205-	L-7/X-206-	L-7/X-207-	L-7/X-208-
	L-7/X-209-	L-7/X-210-	L-7/X-211-	L-7/X-212-	L-7/X-213-	L-7/X-214-
	L-7/X-215-	L-7/X-216-	L-7/X-217-	L-7/X-218-	L-7/X-219-	L-7/X-220-
	L-7/X-221-	L-7/X-222-	L-7/X-223-	L-7/X-224-	L-7/X-225-	L-7/X-226-
25	L-7/X-227-	L-7/X-228-	L-7/X-229-	L-7/X-230-	L-7/X-231-	L-7/X-232-
	L-7/X-233-	L-7/X-234-	L-7/X-235-	L-7/X-236-	L-7/X-237-	L-7/X-238-
	L-7/X-239-	L-7/X-240-	L-7/X-241-	L-7/X-242-	L-7/X-243-	L-7/X-244-
	L-7/X-245-	L-7/X-246-	L-7/X-247-	L-7/X-248-	L-7/X-249-	L-7/X-250-
	L-7/X-251-	L-7/X-252-	L-7/X-253-	L-7/X-254-	L-7/X-255-	L-7/X-256-
30	L-7/X-257-	L-7/X-258-	L-7/X-259-	L-7/X-260-	L-7/X-261-	L-7/X-262-
	L-7/X-263-	L-7/X-264-	L-7/X-265-	L-7/X-266-	L-7/X-267-	L-7/X-268-
	L-7/X-269-	L-7/X-270-	L-7/X-271-	L-7/X-272-	L-7/X-273-	L-7/X-274-
	L-7/X-275-	L-7/X-276-	L-7/X-277-	L-7/X-278-	L-7/X-279-	L-7/X-280-
	L-7/X-281-	L-7/X-282-	L-7/X-283-	L-7/X-284-	L-7/X-285-	L-7/X-286-
35	L-7/X-287-	L-7/X-288-	L-7/X-289-	L-7/X-290-	L-7/X-291-	L-7/X-292-
	L-7/X-293-	L-7/X-294-	L-7/X-295-	L-7/X-296-	L-7/X-297-	L-7/X-298-
	L-7/X-299-	L-7/X-300-	L-7/X-301-	L-7/X-302-	L-7/X-303-	L-7/X-304-
	L-7/X-305-	L-7/X-306-	L-7/X-307-	L-7/X-308-	L-7/X-309-	L-7/X-310-
	L-7/X-311-	L-7/X-312-	L-7/X-313-	L-7/X-314-	L-7/X-315-	L-7/X-316-
40	L-7/X-317-	L-7/X-318-	L-7/X-319-	L-7/X-320-	L-7/X-321-	L-7/X-322-
	L-7/X-323-	L-7/X-324-	L-7/X-325-	L-7/X-326-	L-7/X-327-	L-7/X-328-
	L-7/X-329-	L-7/X-330-	L-7/X-331-	L-7/X-332-	L-7/X-333-	L-7/X-334-
	L-7/X-335-	L-7/X-336-	L-7/X-337-	L-7/X-338-	L-7/X-339-	L-7/X-340-
	L-7/X-341-	L-7/X-342-	L-7/X-343-	L-7/X-344-	L-7/X-345-	L-7/X-346-
45	L-7/X-347-	L-7/X-348-	L-7/X-349-	L-7/X-350-	L-7/X-351-	L-7/X-352-
	L-7/X-353-	L-7/X-354-	L-7/X-355-	L-7/X-356-	L-7/X-357-	L-7/X-358-
	L-7/X-359-	L-7/X-360-	L-7/X-361-	L-7/X-362-	L-7/X-363-	L-7/X-364-
	L-7/X-365-	L-7/X-366-	L-7/X-367-	L-7/X-368-	L-7/X-369-	L-7/X-370-
	L-7/X-371-	L-7/X-372-	L-7/X-373-	L-7/X-374-	L-7/X-375-	L-7/X-376-
50	L-7/X-377-	L-7/X-378-	L-7/X-379-	L-7/X-380-	L-7/X-381-	L-7/X-382-
	L-7/X-383-	L-7/X-384-	L-7/X-385-	L-7/X-386-	L-7/X-387-	L-7/X-388-

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	L-7/X-389-	L-7/X-390-	L-7/X-391-	L-7/X-392-	L-7/X-393-	L-7/X-394-
	L-7/X-395-	L-7/X-396-	L-7/X-397-	L-7/X-398-	L-7/X-399-	L-7/X-400-
	L-7/X-401-	L-7/X-402-	L-7/X-403-	L-7/X-404-	L-7/X-405-	L-7/X-406-
	L-7/X-407-	L-7/X-408-	L-7/X-409-	L-7/X-410-	L-7/X-411-	L-7/X-412-
5	L-7/X-413-	L-7/X-414-	L-7/X-415-	L-7/X-416-	L-7/X-417-	L-7/X-418-

### Pharmaceutical Formulations

When employed as pharmaceuticals, the compounds of the invention are usually administered in the form of pharmaceutical compositions. These compounds can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal. These compounds are effective as both injectable and oral compositions. Such compositions are prepared in a manner well known in the pharmaceutical art and comprise at least one active compound.

This invention also includes pharmaceutical compositions which contain, as the active ingredient, one or more of the compounds of the invention associated with pharmaceutically acceptable carriers. In making the compositions of this invention, the active ingredient is usually mixed with an excipient, diluted by an excipient or enclosed within such a carrier which can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

In preparing a formulation, it may be necessary to mill the active

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compound to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it ordinarily is milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size is normally adjusted by milling to provide a substantially uniform distribution in the formulation, e.g. about 40 mesh.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, sterile water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 5 to about 100 mg, more usually about 10 to about 30 mg, of the active ingredient. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. Preferably, the compound of the invention is employed at no more than about 20 weight percent of the pharmaceutical composition, more preferably no more than about 15 weight percent, with the balance being pharmaceutically inert carrier(s).

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The active compound is effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. It will be understood, however, that the amount of the compound actually administered will be determined by a physician or veterinarian, in the light of the relevant  
5 circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered and its relative activity, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

For preparing solid compositions such as tablets, the principal active  
10 ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally  
15 effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then subdivided into unit dosage forms of the type described above containing from, for example, 0.1 to about 500 mg of the active ingredient of the present invention.

The tablets or pills of the present invention may be coated or otherwise  
20 compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into the  
25 duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids



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and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous  
5 solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as corn oil, cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or  
10 mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described *supra*. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be inhaled  
15 directly from the nebulizing device or the nebulizing device may be attached to a face mask tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

The following formulation examples illustrate representative  
20 pharmaceutical compositions of the present invention.

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Formulation Example 1

Hard gelatin capsules containing the following ingredients are prepared:

5	<u>Ingredient</u>	<u>Quantity</u> <u>(mg/capsule)</u>
	Active Ingredient	30.0
	Starch	305.0
	Magnesium stearate	5.0

The above ingredients are mixed and filled into hard gelatin capsules in 340 mg quantities.

10

Formulation Example 2

A tablet formula is prepared using the ingredients below:

15	<u>Ingredient</u>	<u>Quantity</u> <u>(mg/tablet)</u>
	Active Ingredient	25.0
	Cellulose, microcrystalline	200.0
	Colloidal silicon dioxide	10.0
	Stearic acid	5.0

The components are blended and compressed to form tablets, each weighing 240 mg.

20

Formulation Example 3

A dry powder inhaler formulation is prepared containing the following components:

25	<u>Ingredient</u>	<u>Weight %</u>
	Active Ingredient	5
	Lactose	95

The active ingredient is mixed with the lactose and the mixture is added to a dry powder inhaling appliance.

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Formulation Example 4

Tablets, each containing 30 mg of active ingredient, are prepared as follows:

	<u>Ingredient</u>	<u>Quantity</u> <u>(mg/tablet)</u>
5	Active Ingredient	30.0 mg
	Starch	45.0 mg
	Microcrystalline cellulose	35.0 mg
	Polyvinylpyrrolidone	
10	(as 10% solution in sterile water)	4.0 mg
	Sodium carboxymethyl starch	4.5 mg
	Magnesium stearate	0.5 mg
	Talc	<u>1.0 mg</u>
	Total	120 mg

- 15 The active ingredient, starch and cellulose are passed through a No. 20 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders, which are then passed through a 16 mesh U.S. sieve. The granules so produced are dried at 50° to 60°C and passed through a 16 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and
- 20 talc, previously passed through a No. 30 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 120 mg.

Formulation Example 5

Capsules, each containing 40 mg of medicament are made as follows:

	<u>Ingredient</u>	<u>Quantity</u> <u>(mg/capsule)</u>
25	Active Ingredient	40.0 mg
	Starch	109.0 mg
	Magnesium stearate	<u>1.0 mg</u>
30	Total	150.0 mg

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The active ingredient, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 150 mg quantities.

#### Formulation Example 6

5           Suppositories, each containing 25 mg of active ingredient are made as follows:

<u>Ingredient</u>	<u>Amount</u>
Active Ingredient	25 mg
Saturated fatty acid glycerides to	2,000 mg

10           The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2.0 g capacity and allowed to cool.

#### Formulation Example 7

15           Suspensions, each containing 50 mg of medicament per 5.0 mL dose are made as follows:

	<u>Ingredient</u>	<u>Amount</u>
	Active Ingredient	50.0 mg
	Xanthan gum	4.0 mg
20	Sodium carboxymethyl cellulose (11%)	50.0 mg
	Microcrystalline cellulose (89%)	1.75 g
	Sucrose	10.0 mg
	Sodium benzoate	q.v.
	Flavor and Color	5.0 mL
25	Purified water to	

The active ingredient, sucrose and xanthan gum are blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously made solution of the microcrystalline cellulose and sodium carboxymethyl cellulose in water. The sodium benzoate, flavor, and color are diluted with some of the water

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and added with stirring. Sufficient water is then added to produce the required volume.

Formulation Example 8

5	<u>Ingredient</u>	<u>Quantity</u> <u>(mg/capsule)</u>
	Active Ingredient	15.0 mg
	Starch	407.0 mg
	Magnesium stearate	<u>3.0 mg</u>
	Total	425.0 mg

- 10        The active ingredient, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 425.0 mg quantities.

Formulation Example 9

A formulation may be prepared as follows:

15	<u>Ingredient</u>	<u>Quantity</u>
	Active Ingredient	5.0 mg
	Corn Oil	1.0 mL

Formulation Example 10

A topical formulation may be prepared as follows:

20	<u>Ingredient</u>	<u>Quantity</u>
	Active Ingredient	1-10 g
	Emulsifying Wax	30 g
	Liquid Paraffin	20 g
	White Soft Paraffin	to 100 g

- 25        The white soft paraffin is heated until molten. The liquid paraffin and emulsifying wax are incorporated and stirred until dissolved. The active

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ingredient is added and stirring is continued until dispersed. The mixture is then cooled until solid.

Another preferred formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. See, e.g., U.S. Patent 5,023,252, issued June 11, 1991, herein incorporated by reference. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

Frequently, it will be desirable or necessary to introduce the pharmaceutical composition to the brain, either directly or indirectly. Direct techniques usually involve placement of a drug delivery catheter into the host's ventricular system to bypass the blood-brain barrier. One such implantable delivery system used for the transport of biological factors to specific anatomical regions of the body is described in U.S. Patent 5,011,472, which is herein incorporated by reference.

Indirect techniques, which are generally preferred, usually involve formulating the compositions to provide for drug latentiation by the conversion of hydrophilic drugs into lipid-soluble drugs. Latentiation is generally achieved through blocking of the hydroxy, carbonyl, sulfate, and primary amine groups present on the drug to render the drug more lipid soluble and amenable to transportation across the blood-brain barrier. Alternatively, the delivery of hydrophilic drugs may be enhanced by intra-arterial infusion of hypertonic solutions which can transiently open the blood-brain barrier.

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Other suitable formulations for use in the present invention can be found in *Remington's Pharmaceutical Sciences*, Mace Publishing Company, Philadelphia, PA, 17<sup>th</sup> Ed (1985).

5       The effectiveness of the compounds made according to the invention described herein can be tested for efficacy and affinity by various techniques known in the art. For example, competitive assays with radiolabeled glycine or glutamate may be used to test the efficacy of a multi-binding ligand compound as described herein which includes one or more ligand which is a glutamate or glycine partial agonist or antagonist.

10       Further, the affinity and efficacy of a multi-binding ligand compound as described herein for various potential binding sites on the NMDA receptor can be tested by patch clamp techniques as known in the art. Using such techniques, the affinity of the agonist, partial agonist or antagonist compounds can be measured, as well as the binding kinetics of the compound. Similarly, high throughput  
15       radioligand binding assays can be used to determine the activity of antagonists at any receptor site, and to distinguish between antagonist, partial agonist and agonist activity.

Specifically, the efficacy of the compounds of the invention may be evaluated in a variety of *in vitro* assays as known to those skilled in the art. For  
20       example, the selectivity of compounds for NMDA receptors may be determined according to the method of Kleckner, NW, et al. (1999) 289(2):886. The ability of compounds to inhibit NMDA receptor mediated production of cGMP may be assessed in cultures of cerebral neurons as set forth in Gonzales, JM., et al. *Anesthesiology*, 82(1):205.

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The effectiveness or activity of the compounds can also be tested *in vivo* using several methods well known to those skilled in the art. The analgesic effect of the compounds may be determined in patients with chronic pain according to the methods of Rabben, T., et al. *J. Pharmacol Exp Ther.* (1999) 289(2):1060. The anticonvulsant efficacy of NMDA receptor antagonists may be determined in experimentally induced convulsions and seizures following the methods set forth by Witkin, JM et al. *J. Pharmacol. Exp. Ther.* (1999) 289(2):703 and McDonough, J, et al. *Pharmacol., Biochem. Behav.* (1995) 51(2/3):249. The efficacy of the compounds of the invention on hypoxia may also be evaluated using the method of Schulz et al. as set forth in *Cell Death Differ.* (1998) 10(2):221. The protective effect of compounds on optic nerve degeneration as well as other peripheral neuropathy may be assessed according to the method of Schwartz, M., et al. as set forth in *Euro J. Ophthalmol.* (1999) 9, supplement 1:S9. *In vivo* potency of compounds on motor neuron dysfunction may be tested in mnd mice (Mennini, T, et al. *Eur. J. Neurosci.* (1999) 11(5):1647). The effect of compounds of the invention on a rat model of Parkinsons disease may be evaluated following the method of Piallat, B., et al. (*J Neural Transm* suppl. (1999) 55:71, while the ability of the compounds of the invention to act as behavior modifiers and to enhance memory may be determined in mice (Suzuki, T, et al. *Life Sci.* 64(12):PL151) and rats (Mason, KI., et al. *Brain Res Bull.* 48(1):65).

Other techniques for measuring the efficacy and binding kinetics or affinity of the herein described multi-binding ligand compounds are known to those in the art.

#### Utility

The multibinding agents of the present invention are useful for modulating the NMDA receptor. The modulation of the receptor affects cation transport, particularly calcium and sodium transport. Further, modulation of these receptor



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sites leads to modulation of the effects of excitatory amino acids. These effects are useful in treating mammalian conditions modulated by the NMDA receptor such as pain, but also including, for example, Alzheimer's, cognitive disorder, dementia, schizophrenia, ocular disease, AIDS-related complex, peripheral neuropathy, CV ischemia, infarction, stroke, motor neuron disease, epilepsy, seizure, convulsions, neurodegenerative disease, micturition disorders, migraine, Parkinson's disease, psychosis, Huntingdon's chorea and cardiac failure.

In order to further illustrate the present invention and advantages thereof, the following specific examples are given but are not meant to limit the scope of the claims in any way.

### EXAMPLES

In the Preparations and Examples below, all temperatures are in degrees Celsius (unless otherwise indicated) and all percentages are weight percentages (also unless otherwise indicated).

Preparations 1-57 and Examples 1-23 are given as representative examples of methods for preparing compounds of this invention.

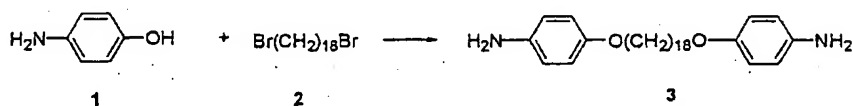
In the Procedures and Examples below, the following abbreviations have the following meanings. If an abbreviation is not defined, it has its generally accepted meaning.

20	Å	= Angstroms
	cm	= centimeter
	DIC	= 2-dimethylaminoisopropyl chloride hydrochloride
	DCC	= <i>N,N</i> -dicyclohexylcarbodiimide
	DCM	= dichloromethane
25	DIPEA	= diisopropylethylamine
	DMA	= <i>N,N</i> -dimethylacetamide

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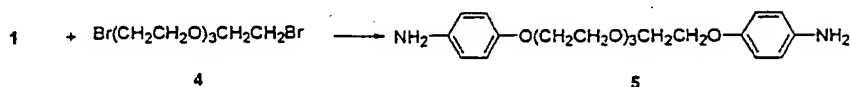
	DMAP	= 4- <i>N,N</i> -dimethylaminopyridine
	DMF	= <i>N,N</i> -dimethylformamide
	DMSO	= dimethylsulfoxide
	DPPA	= diphenylphosphoryl azide
5	g	= gram
	HBTU	= 1-hydroxybenzotriazole
	HPLC	= high performance liquid chromatography
	mg	= milligram
	MIC	= minimum inhibitory concentration
10	min	= minute
	mL	= milliliter
	mm	= millimeter
	mmol	= millimole
	N	= normal
15	PyBOP	= pyridine benzotriazol-1-yloxy-tris(dimethyl-amino)phosphonium hexafluorophosphate
	<i>t</i> -BOC	= <i>tert</i> -butoxycarbonyl
	TBAF	= tetrabutyl ammonium fluoride
	TFA	= trifluoroacetic acid
20	THF	= tetrahydrofuran
	tlc	= thin layer chromatography
	$\mu$ L	= microliters

Preparation 1: 1,18-di(4-aminophenoxy)octadecane, 3.



A mixture of 4-aminophenol (0.25 mol), 1,18-dibromooctadecane (0.125 mol), 2,  $\text{K}_2\text{CO}_3$  (25g) and KI (50 mg) in DMF (100 mL) is heated at 90°. The progress of the reaction is monitored by tlc. When it is complete, the solution is cooled and added to water. The aqueous solution is extracted with ether. The extract is dried and evaporated; the residue is chromatographed to afford 3.

Preparation 2: 1,11-di(4-aminophenoxy)3,6,9-trioxaundecane, 5.



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Using the above procedure, but employing 1,11-dibromo-3,6,9-trioxaundecane, 4, in place of 1,18-dibromooctadecane, there is obtained the product 5.

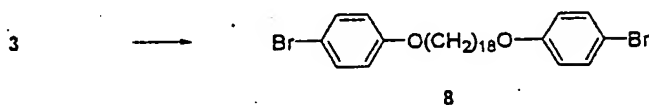
**Preparation 3: 1,4-di(4-isocyanatophenyl)butane, 7, in which X is (CH<sub>2</sub>)<sub>4</sub>. A.**



5            1,4-Di-(4-aminophenyl)butane 6 (0.2 mol) is dissolved in EtOAc (100 mL). Phosgene is bubbled through the EtOAc at 0° until a saturated solution is obtained, and the passage of phosgene is continued for a further hour. The solution is then heated at reflux for two hours, then cooled. A stream of nitrogen is passed through the solution, and it is then filtered. The filtrate is evaporated to afford the  
10            compound 7, in which X is (CH<sub>2</sub>)<sub>4</sub>.

B.        Using the above procedure, but substituting 1,18-di-(4-aminophenoxy) octadecane, 3 or 1,11-di-(4-aminophenoxy)3,6,9-trioxaundecane, 5 for 1,4-(4-aminophenyl)butane, 6, there are obtained respectively the diisocyanates 7, in which X is (CH<sub>2</sub>)<sub>18</sub> or (CH<sub>2</sub>CH<sub>2</sub>O)<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>.

15        **Preparation 4: 1,18-di(4-bromophenoxy)octadecane, 8.**

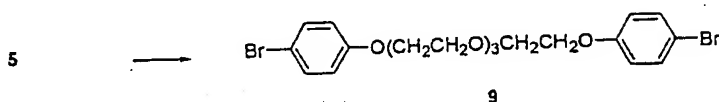


1,18-di(4-aminophenoxy)octadecane, 3, (0.1 mol) is dissolved in concentrated HCl (25 mL) and to the solution is added ice (40 g) and a solution of NaNO<sub>2</sub> (10 g) in water (20 mL). After 1 hour, the excess nitrite is destroyed by the addition of urea, and the solution is filtered. The diazonium chloride solution is

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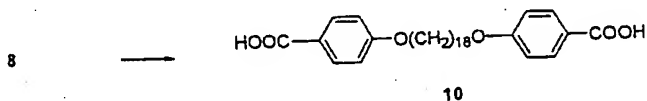
diluted with water (100 mL) and is then added to acetone (400 mL). A solution of CuBr (0.2 mol) and LiBr (0.2 mol) in water (100 mL) is added.. When nitrogen evolution has stopped, the acetone is removed under vacuum and the product is taken up in EtOAc. The EtOAc solution is dried and evaporated, and the residue is chromatographed to afford the dibromide 8.

**Preparation 5: 1,11-di(4-bromophenoxy)-3,6,9-trioxaundecane, 9.**



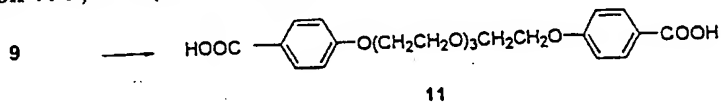
Using the procedure of Preparation 4, but substituting 1,11-di(4-aminophenoxy)-3,6,9-trioxaundecane, 5, for 1,18-di(4-aminophenoxy)octadecane, 3, there is obtained the compound 9.

**Preparation 6: 1,18-di(4-carboxyphenoxy)octadecane, 10.**



1,18-Di(4-bromophenoxy)octadecane, 8, (0.1 mol) is dissolved in dry ether (150 mL). The solution is cooled to  $-78^{\circ}$  and n-BuLi in hexane (0.2 mol) is added. After 1 hour, the solution is warmed to room temperature, and is then added rapidly to dry ice (300 g.). The mixture is allowed to warm to room temperature, and then dilute HCl is added. The mixture is extracted with EtOAc, and the extract is dried and evaporated and the residue is chromatographed to afford the diacid compound 10.

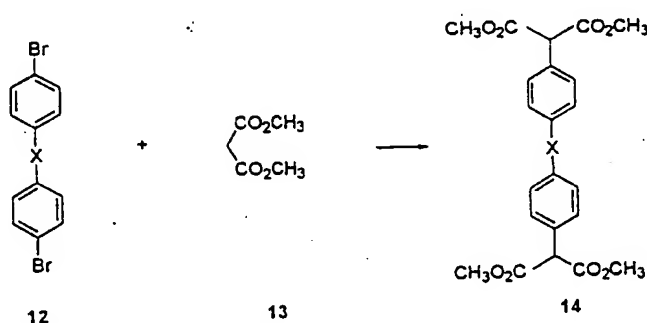
**Preparation 7: 1,11-di(4-carboxyphenoxy)-3,6,9-trioxaundecane, 11.**



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Using the procedure of Preparation 6, but employing 1,11-di-(4-bromophenoxy)-3,6,9-trioxaundecane, **9**, in place of 1,18-di(4-bromophenoxy)octadecane, **8**, there is obtained the diacid compound **11**.

**Preparation 8: 1,4-di-[4-(dicarbomethoxymethyl)phenyl]butane, 14, in which**  
**5 X is (CH<sub>2</sub>)<sub>4</sub>.**

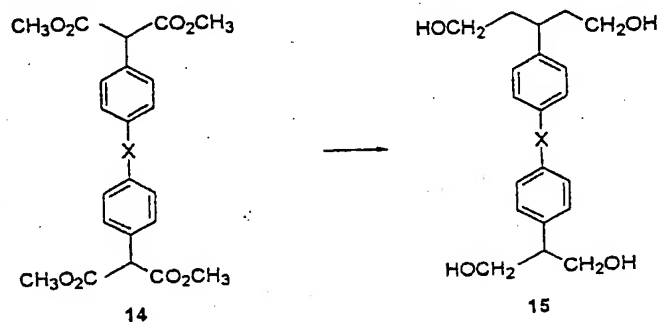


A. Using the procedure described in *Gazz. Chim. Ital.*, 1992, **122**, 511, dimethyl malonate (**13**) (0.2 mol) is dissolved in dioxan (100 mL) and the solution is added dropwise to a suspension of NaH (0.2 mol) in dioxan (100 mL). The temperature is maintained at about 25° by the use of a water bath. When  
**10** hydrogen evolution has ceased, CuBr (0.06 mol) and 1,4-di-(4-bromophenyl)butane (**12**) in which X is (CH<sub>2</sub>)<sub>4</sub>, prepared as described in *Quim. Nova*, 1987, **10**, 102, (0.1 mol) is added. The mixture is heated at reflux for 4 hours, then the solvent is removed under vacuum. Concentrated HCl (50 mL) is added, and the mixture is extracted with toluene. The extract is washed with dilute  
**15** NaHCO<sub>3</sub>, then dried and evaporated. The residue is chromatographed to afford the compound **14**, in which X is (CH<sub>2</sub>)<sub>4</sub>.

B. Using the above procedure, but substituting 1,18-di-(4-bromophenoxy)octadecane, **8**, or 1,11-di-(4-bromophenoxy)-3,6,9-trioxaundecane, **9**, for 1,4-di-(4-bromophenyl)butane, **12**, there are obtained respectively the compounds **14** in  
**20** which X is (CH<sub>2</sub>)<sub>18</sub> or (CH<sub>2</sub>CH<sub>2</sub>O)<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>.

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**Preparation 9: 1,4-di-[4-(di-(1,3-dihydroxyprop-2-yl)phenyl)]butane, 15, in which X is (CH<sub>2</sub>)<sub>4</sub>.**

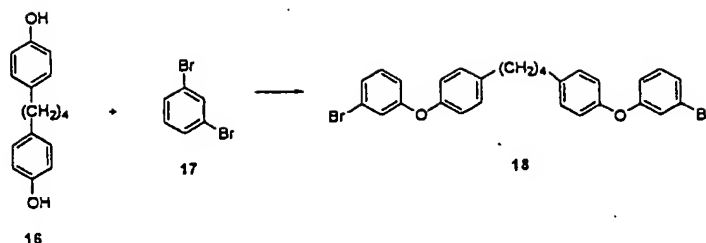


A. Using the procedure described in US Patent 5,091,595, 1,4-di-[4-(dicarbomethoxymethyl)phenyl]butane, **14**, in which X is (CH<sub>2</sub>)<sub>4</sub>, (0.05 mol) is dissolved in dry THF (50 mL) and the solution is added slowly to a solution of diisobutylaluminum hydride (0.25 mol) in THF (100 mL) at 0° under nitrogen. After 1 hour, the mixture is warmed to room temperature. After 3 hours, the mixture is cooled to 0° and MeOH (50 mL) then dilute HCl (0.25 mmol) are added. The pH is adjusted to 9-10 by addition of dilute K<sub>2</sub>CO<sub>3</sub>, and the solution is extracted with EtOAc. The extract is dried and evaporated, and the residue is chromatographed to afford the compound **15**, in which X is (CH<sub>2</sub>)<sub>4</sub>.

B. Using the above procedure, but substituting the compounds **14** in which X is (CH<sub>2</sub>)<sub>18</sub> or (CH<sub>2</sub>CH<sub>2</sub>O)<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub> for **14**, in which X is (CH<sub>2</sub>)<sub>4</sub>, there are obtained respectively the compounds **15**, in which X is (CH<sub>2</sub>)<sub>18</sub> or (CH<sub>2</sub>CH<sub>2</sub>O)<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>.

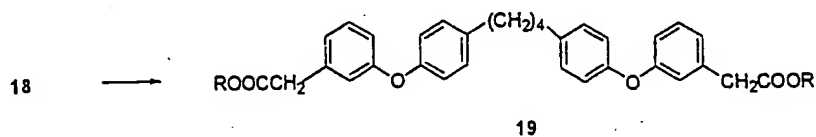
**Preparation 10: 1,4-di-[4-(3-bromophenoxy)phenyl]butane, 18.**

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- Using the procedure described in *J. Amer. Chem. Soc.*, 1987, 119, 10539, 1,3-dibromobenzene, 17, (0.2 mol) and 1,4-di-(4-hydroxyphenyl)butane, 16, prepared as described in *Austral. J. Chem.*, 1993, 46, 277, or European Patent 546639, (0.1 mol) are dissolved in toluene (200 mL) and EtOAc (0.01 mol). To the solution are added  $\text{Cs}_2\text{CO}_3$  (0.4 mol) and copper (I) trifluoromethanesulfonate benzene complex, (0.005 mol). The mixture is heated under reflux and the reaction is monitored by tlc until the reaction is complete. The mixture is cooled and filtered, and the filtrate is evaporated under vacuum. The residue is chromatographed to afford the compound 18.

- 10 **Preparation 11: 1,4-di-[4-[3-(carboxymethyl)phenoxy]phenyl]butane, 19, in which R is H.**



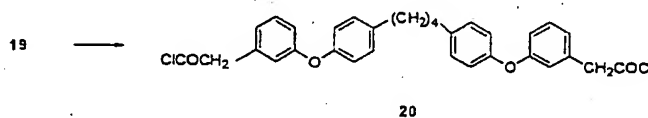
- A. Magnesium (0.2 mol) is placed in a 500 mL round-bottom flask under an inert atmosphere, and dry THF (50 mL) is added. A portion of the solution of the dibromo compound 18 (0.1 mol) in THF (100 mL) and a crystal of iodine are added. When the Grignard reaction has initiated, the remaining amount of the solution of 18 is added, at such a rate as to maintain a gentle reflux. When addition is complete, the solution is allowed to cool, and a solution of anhydrous  $\text{ZnCl}_2$

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(0.2 mol) in dry THF (100 mL) is added. After 2 hours, a solution of methyl bromoacetate (0.2 mol) in dry THF (50 mL) is added. The reaction mixture is heated at reflux for 6 hours, then is cooled and added to dilute HCl. The aqueous mixture is extracted with ether, and the extract is dried and evaporated. The residue is chromatographed to afford the diester product **19**, in which R is methyl.

B. The diester **19** in which R is methyl, (100 mmol) is dissolved in THF (100 mL) and a solution of LiOH, H<sub>2</sub>O (300 mmol) in water (100 mL) is added. The progress of the reaction is monitored by tlc. When it is complete, the mixture is added to dilute HCl and extracted with EtOAc. The extract is dried and evaporated, and the residue is chromatographed to afford the diacid **19**, in which R is H.

**Preparation 12: 1,4-di-[4-[3-(chlorocarbonylmethyl)phenoxy]phenyl]butane, 20.**

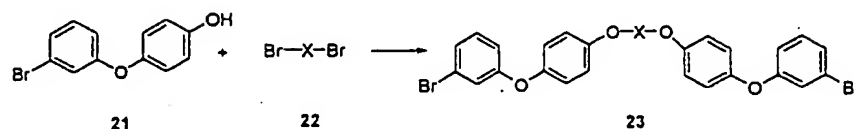


1,4-Di-[4-[3-(carboxymethyl)phenoxy]phenyl]butane, **19**, (0.1 mol) is dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (100 mL). Thionyl chloride (10 mL) and DMF (0.1 mL) are added. After 6 hours, the solvents are removed under vacuum. The residue is redissolved in CH<sub>2</sub>Cl<sub>2</sub> (100 mL), and the solvent is again removed under vacuum to afford the diacid chloride **20**.



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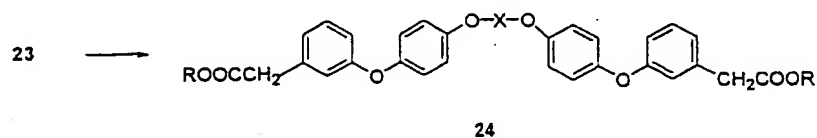
**Preparation 13: 1,18-di-[4-(3-bromophenoxy)phenoxy]octadecane, 23, in which X is  $(\text{CH}_2)_{18}$ .**



A. Using the procedure of Preparation 1, except that 4-(3-bromophenoxy)phenol, **21**, prepared as described in *J. Labelled Compds. Radiopharm.*, 1980, **25**, 1007, is used in place of 4-aminophenol, **1**, there is obtained the compound **23**, in which X is  $(\text{CH}_2)_{18}$ .

B. Using the procedure of Preparation 13A, except that 1,11-dibromo-3,6,9-trioxaundecane **9** is used in place of 1,18-dibromooctadecene **22**, there is obtained the compound 1,11-di-[4-(3-bromophenoxy)phenoxy]-3,6,9-trioxaundecane **23**, in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .

**Preparation 14: 1,18-di-[4-[3-(carboxymethyl)phenoxy]phenoxy]octadecane, 24, in which X is  $(\text{CH}_2)_{18}$ .**

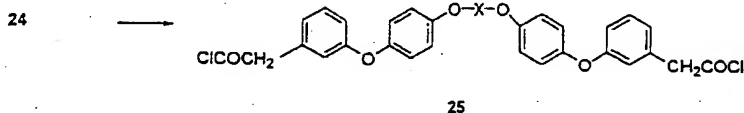


A. Using the procedure of Preparation 11, 1,18-di-[4-(3-bromophenoxy)phenoxy]-octadecane, **23**, in which X is  $(\text{CH}_2)_{18}$ , is converted into **24**, in which X is  $(\text{CH}_2)_{18}$  and R is H.

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B. Using the procedure of Preparation 11, 1,11-di-[4-(3-bromophenoxy)phenoxy]-3,6,9-trioxaundecane **23**, in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$  is converted into the compound **24**, in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$  and R is H.

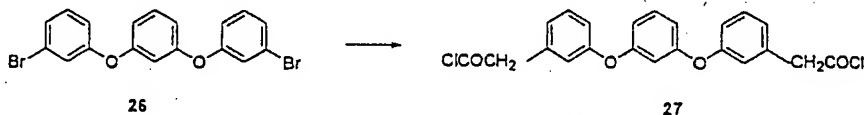
5 Preparation 15: 1,18-di-[4-[3-(chlorocarbonylmethyl)phenoxy]octadecane, **25**, in which X is  $(\text{CH}_2)_{18}$ .



A. Using the procedure of Preparation 12, 1,18-di-[4-[3-(carboxymethyl)phenoxy]phenoxy]octadecane, **24**, in which X is  $(\text{CH}_2)_{18}$  and R is H is converted into **25**, in which X is  $(\text{CH}_2)_{18}$ .

10 B. Using the procedure of Preparation 12, the compound **24**, in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$  and R is H, is converted in to the compound **25**, in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .

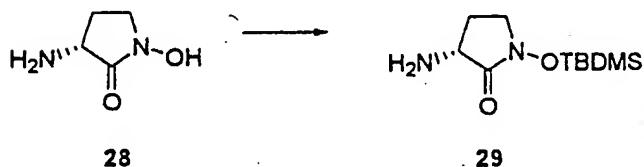
Preparation 16: 1,3-di-[3-(chlorocarbonylmethyl)phenoxy]benzene, **27**.



15 Using the procedures of Preparations 11 and 12, 1,3-di(3-bromophenoxy)benzene, **26**, prepared as described in *Polym. Sci. Technol.*, 1984, **25**, **24**, or US Patent 3,5567,783, is converted into the diacid chloride compound **27**.

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Preparation 17: 3-(R)-amino-1-(tert-butyldimethylsilyloxy)-2-pyrrolidinone, 29.



3-(R)-Amino-1-hydroxy-2-pyrrolidinone, 28 (HA 966) (50 mmol) is dissolved in CH<sub>2</sub>Cl<sub>2</sub> (50 mL), and triethylamine (250 mmol) and tert-butyldimethylsilyl chloride (55 mmol) are added. The progress of the reaction is monitored by tlc. When it is complete, the solution is washed with water, then dried and evaporated to afford the silylated compound 29.

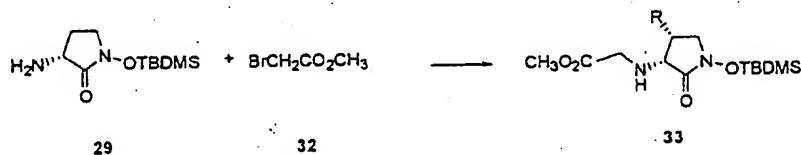
Preparation 18. 3-(R)-amino-1-(tert-butyldimethylsilyloxy)-4-(R)-methyl-2-pyrrolidinone, 31.



Using the procedure of Preparation 17, 3-(R)-amino-1-hydroxy-4-(R)-methyl-2-pyrrolidinone, 30, prepared as described in *Tetrahedron*, 1995, 51, 115821, is converted into the compound 31.

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**Preparation 19.** Alkylation of 3-(R)-amino-1-(tert-butyldimethylsilyloxy)-2-pyrrolidinone, **29**, with methyl bromoacetate, to afford the aminoester **33**, in which R is H.



- A. Methyl bromoacetate, **32**, (50 mmol) and  $\text{K}_2\text{CO}_3$  (2.0g) are added to a solution of **29** (45 mmol) in DMF (25 mL). The mixture is heated to  $50^\circ$ . The progress of the reaction is monitored by tlc. When it is complete, the solution is cooled and added to water. The aqueous solution is extracted with EtOAc. The extract is dried and evaporated and the residue is chromatographed to afford the compound **33**, in which R is H.
- 10 B. Using the above procedure, but employing the amine **31** in place of **29**, there is obtained the aminoester **33**, in which R is methyl.

**Preparation 20.** Hydrolysis of the aminoester **33** to the acid **34**.



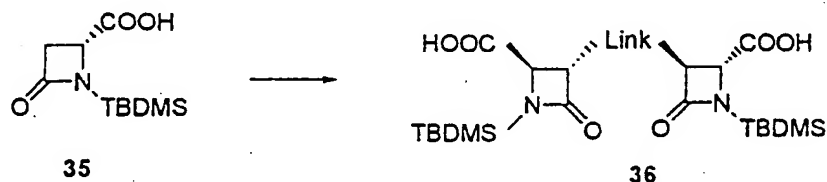
- A. The aminoester **33**, in which R is H, (50 mmol) is dissolved in THF (10 mL) and water (5 mL). A solution of LiOH,  $\text{H}_2\text{O}$  (55 mmol) in water (5 mL) is added. The progress of the reaction is followed by tlc. When it is complete, the mixture is added to water. The pH is adjusted to 7 by addition of aqueous  $\text{NaH}_2\text{PO}_4$ , and the solution is extracted with  $\text{CH}_2\text{Cl}_2$ . The extract is dried and
- 15

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evaporated, and the residue is chromatographed to afford the compound **34** in which R is H.

B. Using the above procedure, the aminoester **33**, in which R is methyl, is converted into the compound **34**, in which R is methyl.

- 5 **Preparation 21.** Alkylation of the azetidinone **35** with 1,4-diiodobutane to afford the dimeric product **36**, in which Link is  $(\text{CH}_2)_4$ .



- 10 A solution of lithium diisopropylamide (80 mmol) in THF (50 mL) is added with stirring to a solution of (4R)-N-tert-butyldimethylsilylazetidin-2-one-3-carboxylic acid, **35**, prepared as described in *Tetrahedron*, 1990, **46**, 4733, (35 mmol) in THF (50 mL) at  $0^\circ$ . After 15 minutes, 1,4-diiodobutane (40 mmol) is added. The progress of the reaction is followed by tlc. When it is complete, the mixture is added to aqueous  $\text{KHSO}_4$  and extracted with EtOAc. The extract is dried and evaporated and the residue is chromatographed to afford the product **36**, in which Link is  $(\text{CH}_2)_4$ .

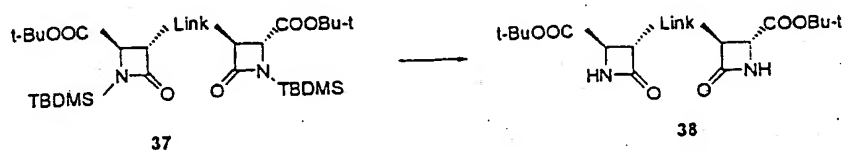
- 15 **Preparation 22:** Conversion of the bis (azetidinone carboxylic acid) **36** to the corresponding ditertiary butyl ester **37**, in which Link is  $(\text{CH}_2)_4$ .



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The dicarboxylic acid **36**, in which Link is  $(\text{CH}_2)_4$ , (50 mmol) is dissolved in 1:1  $\text{CH}_2\text{Cl}_2$ :cyclohexane (100 mL) and to the solution is added  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  (25 mL) and then tert-butyl trichloroacetimidate (200 mmol). The progress of the reaction is monitored by tlc. When it is complete, solid  $\text{NaHCO}_3$  (20 g) is added and the volatiles are removed under vacuum. The residue is dissolved in  $\text{CH}_2\text{Cl}_2$ , and the solution is washed and dried. The residue is chromatographed to afford the diester **37**, in which Link is  $(\text{CH}_2)_4$ .

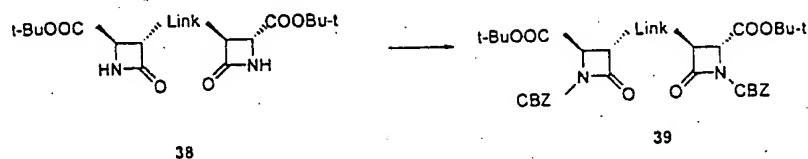
**Preparation 23: Desilylation of the diester **37**, to afford **38**, in which Link is  $(\text{CH}_2)_4$ .**



The diester **37**, in which Link is  $(\text{CH}_2)_4$ , (30 mmol) is dissolved in MeOH (50 mL) and CsF (50 mmol) is added. After 3 hours,  $\text{CH}_2\text{Cl}_2$  (100 mL) is added. The mixture is washed with water, then dried and evaporated. The residue is chromatographed to afford the dimeric amide **38**, in which Link is  $(\text{CH}_2)_4$ .

**Preparation 24: Conversion of **38** to the bis-BOC-protected azetidinone **39**, in which Link is  $(\text{CH}_2)_4$ .**

Preparation 24

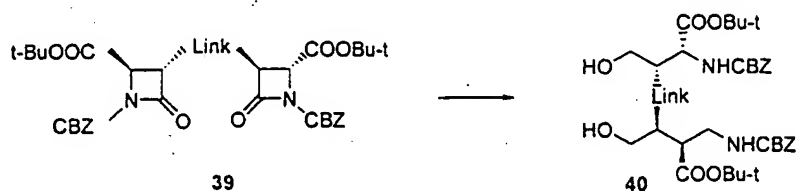


Compound **38**, in which Link is  $(\text{CH}_2)_4$ , (10 mmol) is dissolved in MeCN (50 mL) and *p*-chlorobenzoylchloride (250 mmol) and 4-dimethylaminopyridine (3 mmol) are added. The progress of the reaction is monitored by tlc. When it is

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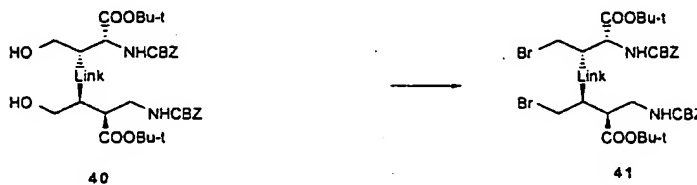
complete, the mixture is diluted with  $\text{CH}_2\text{Cl}_2$  (100 mL). The solution is washed with dilute  $\text{KHSO}_4$ , then dried and evaporated. The residue is chromatographed to afford compound 39, in which Link is  $(\text{CH}_2)_4$ .

**Preparation 25: Reductive ring-opening of the azetidinone 39 to afford the diol 40, in which Link is  $(\text{CH}_2)_4$ .**

**Preparation 25**

The azetidinone 39, in which Link is  $(\text{CH}_2)_4$ , (5 mmol) is dissolved in MeOH (25 mL) at  $0^\circ$ , and  $\text{NaBH}_4$  (15 mmol) is added. The progress of the reaction is monitored by tlc. When it is complete, silica gel (20 g) is added, the mixture is filtered and the solvent is removed under vacuum. The residue is chromatographed to afford the diol 40, in which Link is  $(\text{CH}_2)_4$ .

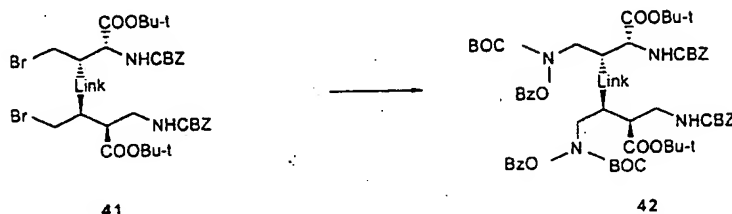
**Preparation 26: Conversion of the diol 40 to the dibromide 41, in which Link is  $(\text{CH}_2)_4$ .**

**Preparation 26**

The diol 40, in which Link is  $(\text{CH}_2)_4$ , (5 mmol) is dissolved in  $\text{CH}_2\text{Cl}_2$  (10 mL) at  $0^\circ$ , and  $\text{CBr}_4$  (12 mmol) is added. A solution of  $\text{PPh}_3$  (15 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL) is added. The progress of the reaction is monitored by tlc. When it is complete, the solvent is removed under vacuum, and the residue is chromatographed to afford the dibromide 41, in which Link is  $(\text{CH}_2)_4$ .

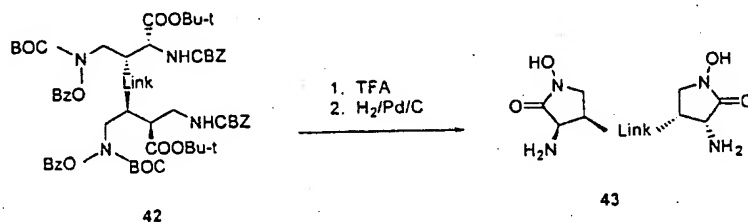
-104-

**Preparation 27:** Displacement reaction of the dibromide 41 with BOCNHOCH<sub>2</sub>Ph to afford the amino product 42, in which Link is (CH<sub>2</sub>)<sub>4</sub>.

**Preparation 27**

The dibromo compound 41, in which Link is (CH<sub>2</sub>)<sub>4</sub>, (1 mmol) is dissolved in DMF (10 mL), and K<sub>2</sub>CO<sub>3</sub> (2 mmol), KI (0.02 mmol) and BOCNHOCH<sub>2</sub>Ph (8 mmol) are added to the solution. The progress of the reaction is monitored by tlc. When it is complete, the mixture is diluted with water and extracted with ether. The extract is dried and evaporated, and the residue is chromatographed to afford the compound 42, in which Link is (CH<sub>2</sub>)<sub>4</sub>.

**Preparation 28:** Deprotection and cyclization of the ditertiary butyl ester 42, to afford the bis-(pyrrolidinone) 43, in which Link is (CH<sub>2</sub>)<sub>4</sub>.

**Preparation 28**

A. Compound 42, in which Link is (CH<sub>2</sub>)<sub>4</sub>, (1 mmol) is dissolved in TFA (10 mL). The progress of the reaction is monitored by tlc. When it is complete, the TFA is removed under vacuum. The residue is dissolved in methanol, treated with 10% Pd/C, and hydrogenated at 40 psi H<sub>2</sub> for 24 hours. The mixture is filtered through a pad of celite and the filtrate is concentrated under reduced pressure.

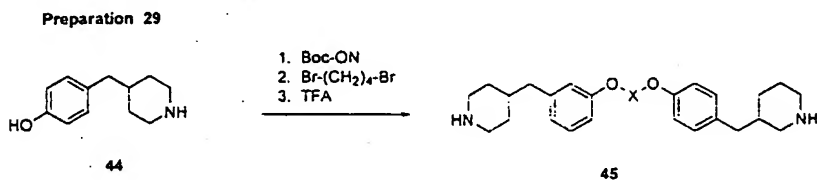


-105-

The residue is chromatographed to afford the compound **43**, in which Link is  $(\text{CH}_2)_4$ .

- B. Using the procedures of Preparations 21-28, but employing in Preparation 21 different dialkylating agents, as described herein, in place of 1,4-diiodobutane, there are obtained different bis-(pyrrolidinones) **43**, for example those in which Link is  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .

**Preparation 29: Dialkylation of 1,4-dibromobutane with 4-(4-hydroxybenzyl)piperidine, **44** to yield diether **45**.**



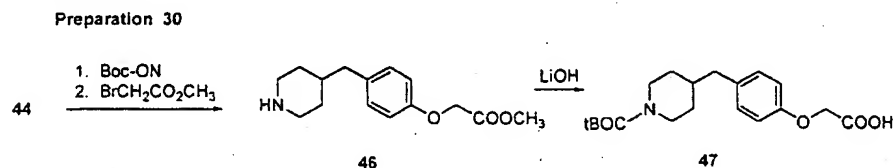
- A. 4-(4-Hydroxybenzyl)piperidine, prepared as described in Oyo Yakuri, 1975, 10, 841-8. (0.2 mol) is dissolved in  $\text{CH}_2\text{Cl}_2$  (200 mL). BOC-ON= $\text{C}(\text{CN})\text{Ph}$ , obtained from the Aldrich Chemical Co., (0.22 mol) and  $\text{Et}_3\text{N}$  (0.50 mol) are added and the progress of the reaction is monitored by tlc. When it is complete, the solution is washed with dilute HCl, then dried and evaporated to afford crude Boc 4-(4-hydroxybenzyl)piperidine, which is purified by chromatography.
- B. Boc 4-(4-hydroxybenzyl)piperidine (0.1 mol) is dissolved in DMF (50 mL) containing  $\text{K}_2\text{CO}_3$  (2.5 g) KI (50 mg) and 1,4-dibromobutane (0.05 mol). The mixture is stirred and the progress of the reaction is monitored by tlc. When it is complete, the mixture is added to water and extracted with EtOAc. The extract is washed, dried and evaporated; and the residue is chromatographed to afford the di-Boc protected form of diether **45**, in which X is  $(\text{CH}_2)_4$ .

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C. Di-Boc 45 (1 mmol) is dissolved in TFA (10 mL). The progress of the reaction is monitored by tlc. When it is complete, the TFA is removed under vacuum, the residue is chromatographed to afford the compound 45, in which X is  $(\text{CH}_2)_4$ .

- 5 D. In a similar manner, by employing different dialkylating agents, as described herein, such as 1,18-dibromooctadecane or 1,11-dibromo-3,6,9-trioxaundecane, in place of 1,4-dibromobutane, there are obtained the compounds 45 in which X is  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .

10 Preparation 30: Alkylation of 4-(4-hydroxybenzyl)piperidine, 44, with methyl bromoacetate, and N-protection and ester hydrolysis of the product, to afford the acid 47.



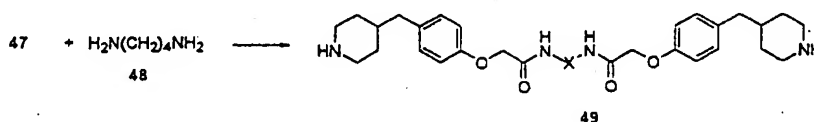
- A. 4-Hydroxybenzyl)piperidine (0.2 mol) is dissolved in  $\text{CH}_2\text{Cl}_2$  (200 mL) BOC-ON= $\text{C}(\text{CN})\text{Ph}$ , obtained from the Aldrich Chemical Co., (0.22 mol) and  $\text{Et}_3\text{N}$  (0.50 mol) are added and the progress of the reaction is monitored by tlc.
- 15 When it is complete, the solution is washed with dilute HCl, then dried and evaporated. Boc 4-hydroxybenzyl)piperidine is purified by chromatography.

- B. Boc 4-hydroxybenzyl)piperidine (0.1 mol) is dissolved in DMF (50 mL) and  $\text{K}_2\text{CO}_3$  (5 g) and methyl bromoacetate (0.1 mol) are added. The mixture is stirred and the progress of the reaction is monitored by tlc. When it is complete,
- 20 the mixture is added to water and extracted with EtOAc. The extract is washed, dried and evaporated, and the residue is chromatographed too afford the

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intermediate compound 46. The residue is dissolved in THF (100 mL) and a solution of LiOH, H<sub>2</sub>O (0.11 mol) in water (100 mL) is added. The mixture is stirred and the progress of the reaction is monitored by tlc. When it is complete, the mixture is added to dilute HCl and extracted with EtOAc. The extract is washed, dried and evaporated, and the residue is chromatographed to afford the Boc protected acetic acid compound 47.

**Preparation 31: Acylation of 1,4-diaminobutane, 48, with the acetic acid 47, and removal of the BOC group to afford the intermediate 49, in which X is (CH<sub>2</sub>)<sub>4</sub>.**

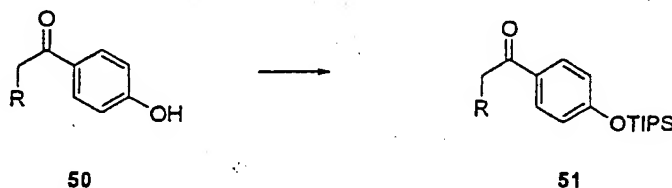


- 10 A. The acetic acid 47 (50 mmol) and dicyclohexylcarbodiimide (50 mmol) are dissolved in CH<sub>2</sub>Cl<sub>2</sub> (100 mL), and 1,4-diaminobutane, 48, (25 mmol) is added. The progress of the reaction is monitored by tlc. When it is complete, the solution is washed with dilute HCl, then dried and evaporated. The residue is dissolved in 3M HCl in EtOAc (50 mL). After 30 minutes the solvent is removed under vacuum and the residue is chromatographed to afford the compound 49, in which X is (CH<sub>2</sub>)<sub>4</sub>.
- 15

B. Using the above procedure, but employing other diamines as described herein in place of 1,4-diaminobutane, there are obtained the corresponding compounds of the general structure 49.

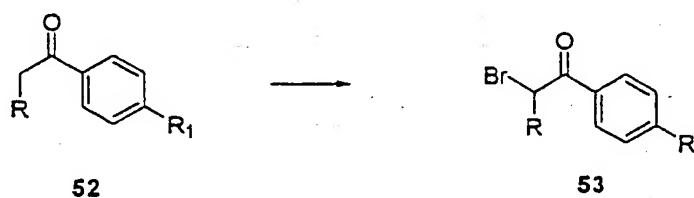
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**Preparation 32:** Silylation of 4-hydroxypropiophenone, 50, to afford 4-triisopropylsilyloxyacetophenone, 51, in which R is methyl.



4-Hydroxypropiophenone, 50, when R is methyl, (0.1 mol) is dissolved in DMF (50 mL) and Et<sub>3</sub>N (0.11 mol) and chlorotriisopropylsilane (0.11 mol) are added. The mixture is stirred and the progress of the reaction is monitored by tlc. When it is complete, the mixture is added to water and extracted with EtOAc. The extract is washed, dried and evaporated, and the residue is chromatographed to afford the intermediate compound 51 in which R is methyl.

**Preparation 33:** Bromination of acetophenones and propiophenones to afford the bromoketones 53.

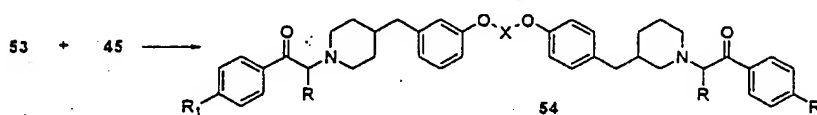


A. Compound 52 in which R is methyl and R<sub>1</sub> is triisopropylsilyloxy (0.1 mol) is dissolved in CCl<sub>4</sub> (100 mL) and the solution is heated to reflux. Bromine (0.1 mol) is added at such a rate that it is absorbed immediately. The solution is cooled and the solvent is removed under vacuum to afford the product 53, in which R is methyl and R<sub>1</sub> is triisopropylsilyloxy.

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B. Using the above procedure, 4-chloroacetophenone, **52**, in which R is H and R<sub>1</sub> is Cl is converted into **53** in which R is H and R<sub>1</sub> is Cl.

**Preparation 34: Alkylation of bromoacetophenones **53** with dimeric piperidine derivatives **45**, to afford the intermediate compounds **54**.**

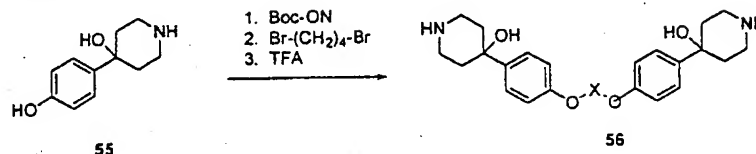


- 5 A. The  $\alpha$ -bromopropiophenone **53** in which R is methyl and R<sub>1</sub> is triisopropylsilyloxy (50 mmol), the piperidine **45**, in which X is (CH<sub>2</sub>)<sub>4</sub>, (25 mmol) and Et<sub>3</sub>N (100 mmol) are dissolved in EtOH (50 mL). The solution is heated under reflux. The progress of the reaction is monitored by tlc. When it is complete, the mixture is added to water and extracted with EtOAc. The extract is
- 10 dried and evaporated and the residue is chromatographed to afford the compound **54**, in which X is (CH<sub>2</sub>)<sub>4</sub>, R is methyl and R<sub>1</sub> is triisopropylsilyloxy.
  
- B. Using the same procedure,  $\alpha$ -bromo-4-chloroacetophenone **53**, in which R is H and R<sub>1</sub> is Cl, is reacted with the piperidine **45**, in which X is (CH<sub>2</sub>)<sub>4</sub>, to afford the intermediate compound **54**, in which X is (CH<sub>2</sub>)<sub>4</sub>, R is H and R<sub>1</sub> is Cl.
  
- 15 C. Using the procedures of A and B above, but employing piperidines **45** in which X is (CH<sub>2</sub>)<sub>18</sub> or (CH<sub>2</sub>CH<sub>2</sub>O)<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>, there are obtained the corresponding compounds **54** in which X is (CH<sub>2</sub>)<sub>18</sub> or (CH<sub>2</sub>CH<sub>2</sub>O)<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>.

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**Preparation 35: Alkylation of 1,4-dibromobutane to afford the diether 56, in which X is  $(\text{CH}_2)_4$ .**

Preparation 35

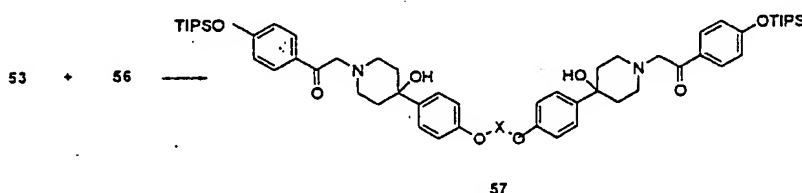


- A. 4-(4-hydroxyphenyl)-4-hydroxypiperidine **55**, prepared as described in European Patent 474561 (0.2 mol) is dissolved in  $\text{CH}_2\text{Cl}_2$  (200 mL) BOC-ON= $\text{C}(\text{CN})\text{Ph}$ , obtained from the Aldrich Chemical Co., (0.22 mol) and  $\text{Et}_3\text{N}$  (0.50 mol) are added and the progress of the reaction is monitored by tlc. When it is complete, the solution is washed with dilute HCl, then dried and evaporated. Boc 4-(4-hydroxyphenyl)-4-hydroxypiperidine is purified by chromatography.
- B. Boc 4-(4-hydroxyphenyl)-4-hydroxypiperidine (100 mmol) is added to DMF (100 mL) containing  $\text{K}_2\text{CO}_3$  (5 g), KI (50 mg) and 1,4-dibromobutane (55 mmol). The mixture is stirred and the progress of the reaction is monitored by tlc. When it is complete, the mixture is added to water and extracted with EtOAc. The extract is washed, dried and evaporated, and the residue is chromatographed to afford the di-Boc protected form of compound **56**, in which X is  $(\text{CH}_2)_4$ .
- C. Di-Boc **56** (1 mmol) is dissolved in TFA (10 mL). The progress of the reaction is monitored by tlc. When it is complete, the TFA is removed under vacuum, and the residue is chromatographed to afford the compound **56**, in which X is  $(\text{CH}_2)_4$ .
- D. Using the above procedure, but employing different dialkylating agents, as described herein, in place of 1,4-dibromobutane, there are obtained the

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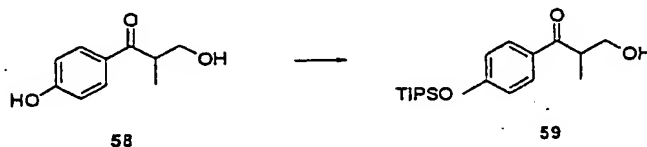
corresponding compounds **56**, for example in which X is  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .

**Preparation 36: Reaction between the hydroxypiperidine compound **56** and the bromoketone **53** to afford the dimeric intermediate **57**, in which X is  $(\text{CH}_2)_4$ .**



- 5 A. Using the procedure of Preparation 34A, but employing the bromoketone **53** in which R is H and  $\text{R}_1$  is triisopropylsilyloxy, and the piperidine **56** in which X is  $(\text{CH}_2)_4$ , there is obtained the dimeric intermediate compound **57**, in which X is  $(\text{CH}_2)_4$ .
- 10 B. Using the above procedure, but employing compounds **56** in which X is  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ , there are obtained the corresponding compounds **57** in which X is  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .

**Preparation 37: Silylation of 3',4-dihydroxy-2'-methylpropiophenone, **58**, to afford the intermediate compound **59**.**



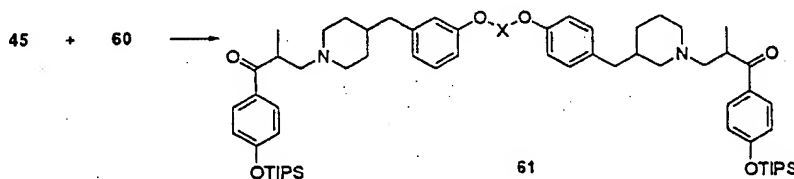
- 15 Using the procedure of Preparation 32, 3',4-dihydroxy-2'-methylpropiophenone, **58**, prepared as described in *Synthesis*, 1984, 4, 339-42, is converted into the silyl ether **59**.

**Preparation 38: Tosylation of the silyl ether 59 to afford the compound 60.**



The alcohol **59** (100 mmol) is dissolved in pyridine (50 mL) and p-toluenesulfonyl chloride (105 mmol) is added. The mixture is stirred and the progress of the reaction is monitored by tlc. When it is complete, the mixture is added to water and extracted with EtOAc. The extract is washed with dilute HCl, then dried and evaporated to afford the toluenesulfonate compound **60**.

**Preparation 39: Alkylation of the toluenesulfonate 60 with the piperidine 45, to afford the dimeric intermediate 61, in which X is  $(CH_2)_4$ .**



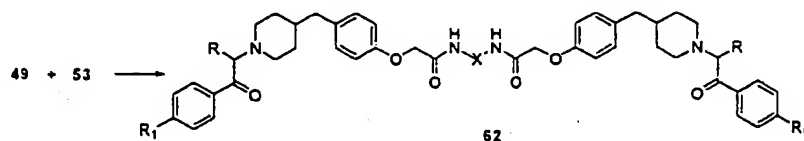
10 A. The dimeric piperidine **45**, in which X is  $(\text{CH}_2)_4$  (50 mmol) is dissolved in DMF (50 mL) containing  $\text{K}_2\text{CO}_3$  (5 g), and the tosylate ester **60** (100 mmol) is added. The progress of the reaction is monitored by tlc. When it is complete, the mixture is added to water and extracted with EtOAc. The extract is washed with dilute HCl, then dried and evaporated. The residue is chromatographed to afford the compound **61**, in which X is  $(\text{CH}_2)_4$ .

15. B. Using the above procedure, but employing the piperidine compounds **45** in which X is  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ , there are obtained the corresponding compounds **61**, in which X is  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .



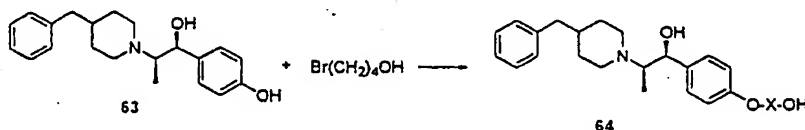
-113-

**Preparation 40:** Alkylation of the amide-linked piperidine intermediate **49** to afford the compound **62** in which X is  $(\text{CH}_2)_4$ .



- A. Using the procedure of Preparation 34, the bromoketones **53**, in which R is H or methyl and  $R_1$  is triisopropylsilyloxy or chloro, are reacted with the piperidine **49** in which X is  $(\text{CH}_2)_4$ , to afford the compounds **62**, in which X is  $(\text{CH}_2)_4$ , R is H or methyl, and  $R_1$  is triisopropylsilyloxy or chloro.
- B. Using the above procedure, but employing the piperidine compounds **49** in which X is  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ , there are obtained the corresponding compounds **62** in which X is  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ , R is H or methyl, and  $R_1$  is chloro or triisopropylsilyloxy.

**Preparation 41:** Alkylation of Ifenprodil, **63**, with 4-bromobutanol, to afford the alcohol **64** in which X is  $(\text{CH}_2)_4$ .



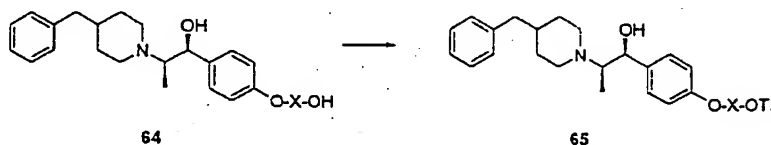
- A. Using the conditions of Preparation 1. Ifenprodil, **63**, prepared as described in *J. Med. Chem.*, 1995, **38**, 3138, and 4-bromobutanol are reacted together to afford the alcohol **64**, in which X is  $(\text{CH}_2)_4$ .
- B. Using the above procedure, but employing different bromo alcohols, as described herein, such as 18-bromooctadecanol, or 1-bromo-11-hydroxy-3,6,9-

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trioxaundecane, there are obtained the corresponding compounds **64** in which X is  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .

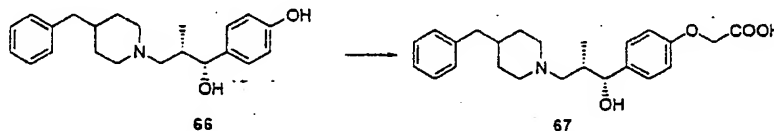
- C. Using the above procedures, but employing, for example, RO-25-6981, **66**, prepared as described in Canadian Patent 2129771, or Nylidrin (**104**), prepared as described in German Patent DE 3037163, or CP-101606, (**102**) prepared as described in *J. Med. Chem.*, 1995, **38**, 3138-45, there are obtained the alkylated products analogous to **64**.

**Preparation 42: Conversion of the alcohol **64**, in which X is  $(\text{CH}_2)_4$ , to the tosylate **65**, in which X is  $(\text{CH}_2)_4$ .**



- 10 A. Using the conditions of Preparation 38; the alcohol **64**, in which X is  $(\text{CH}_2)_4$ , is converted into the tosylate **65**, in which X is  $(\text{CH}_2)_4$ .
- B. Using the above conditions, the alcohols whose preparations are described in Preparation 41B and 41C are converted into the corresponding tosylates.

- 15 **Preparation 43: Alkylation of RO-25-6981, **66**, with methyl bromoacetate, and hydrolysis of the product to afford the phenoxyacetic acid **67**.**

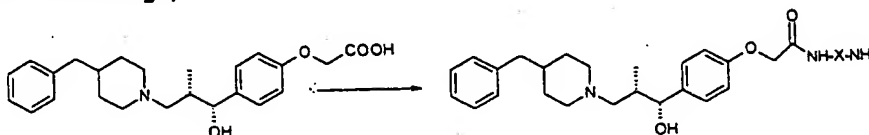


- A. Using the conditions of Preparation 30, RO-25-6981, **66**, is converted into the acid **67**.

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B. Using the above conditions, Ifenprodil, (63) Nylidrin (104) or CP-101606 (102) or the like are converted into the analogous phenoxyacetic acids.

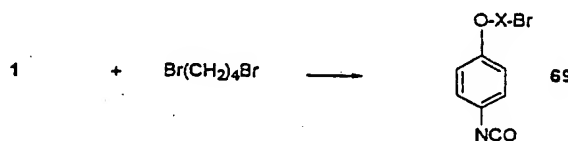
**Preparation 44: Amination of the acetic acid 67 to afford the amide 68, in which X is  $(\text{CH}_2)_4$ .**



- 5 A. The acetic acid 67, in which X is  $(\text{CH}_2)_4$  (100 mmol) is dissolved in DMF (100 mL) and dicyclohexylcarbodiimide (100 mmol) is added, followed by 1,4-diaminobutane (500 mmol). The progress of the reaction is followed by tlc. When it is complete, the mixture is added to water and extracted with EtOAc. The extract is dried and evaporated and the residue is chromatographed to afford the
- 10 aminoamide 68, in which X is  $(\text{CH}_2)_4$ .
  
- B. Using the same procedure, but employing different aminoalcohols, such as 18-amino-octadecanol, or 1-amino-11-hydroxy-3,6,9-trioxaundecane, there are obtained the corresponding compounds 68 in which X is  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .
  
- 15 C. Using the procedures A and B above, but employing as starting materials the phenoxyacetic acids described in Preparation 43B, the analogous aminoamides are obtained.

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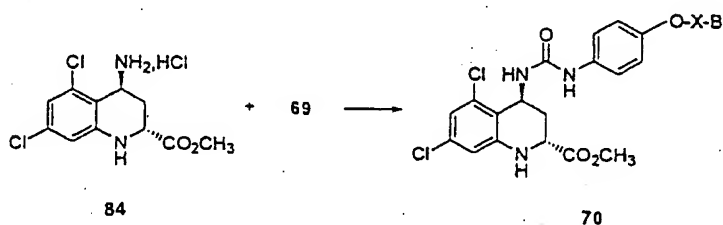
Preparation 45: 1-bromo-4-(4-isocyanatophenoxy)butane, **69**, in which X is  $(\text{CH}_2)_4$ .



A. Using the conditions of preparation 1, equimolar amounts of **1** and 1,4-dibromobutane are reacted to afford after chromatography 4-(4-aminophenoxy)-1-bromobutane. This compound is treated under the conditions of Preparation 3 to afford the isocyanate **69**, in which X is  $(\text{CH}_2)_4$ .

B. In a similar manner, the compounds **69** in which X is  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$  are prepared.

Preparation 46: Reaction of the isocyanate **69** with the 4-aminotetrahydroquinoline **84** to afford the urea intermediate **70** in which X is  $(\text{CH}_2)_4$ .

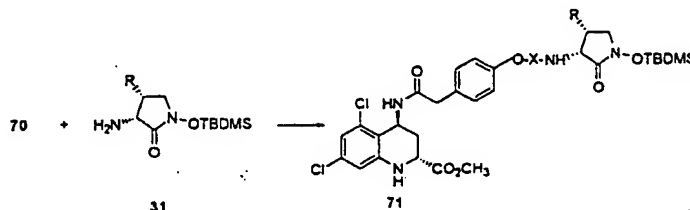


A. Using the conditions of Example 1A, the isocyanate **69** is reacted with the amine **84** to afford the urea **70** in which X is  $(\text{CH}_2)_4$ .

B. In a similar manner, the products of Preparation 45B are converted into the ureas **70** in which X is  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .

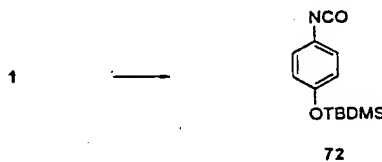
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**Preparation 47:** Alkylation of the bromo compound 70 with amines derived from HA-966 and L-687414, 31, to give the intermediate 71 in which X is  $(\text{CH}_2)_4$ .



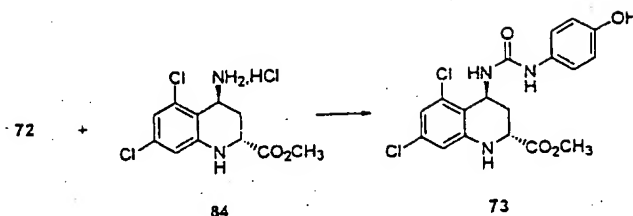
- A. Using the conditions of Preparation 29, the silyl-protected amine 31, in which R is H, is reacted with the bromo compound 70, to afford the amine 71, in which X is  $(\text{CH}_2)_4$  and R is H.
- B. Using the above conditions, but employing the bromo compounds 70 in which X is  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ , there are obtained the corresponding compounds 71 in which X is  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .
- C. Using the conditions of A and B above, but employing the amine 31 in which R is methyl, there are obtained the compounds 71 in which R is methyl.

**Preparation 48:** 1-tert-butyldimethylsilyloxy-4-isocyanatobenzene, 72.



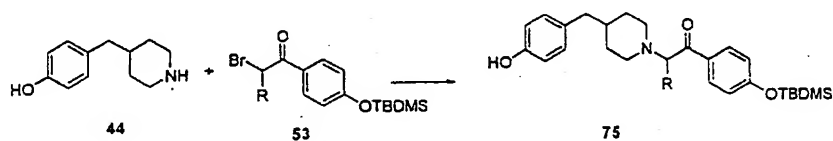
Using the procedure of Preparation 17, followed by the procedure of Preparation 3, 4-aminophenol, 1, is converted into the compound 72.

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**Preparation 49: 4-hydroxyphenylurea 73.**

Using the procedure of Example 1, the isocyanate **72** is reacted with the amine **84** to afford the silyl-protected ureas. This material is dissolved in THF. and Bu<sub>4</sub>NF (2 mole eq) in THF is added. After 1 hour, the mixture is added to  
5 water and extracted with EtOAc. The extract is dried and evaporated to afford the compound **73**.

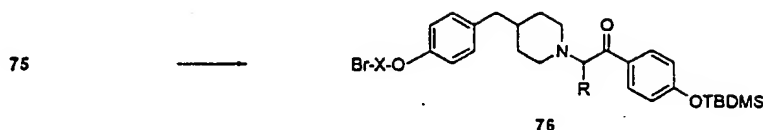
**Preparation 50: Reaction of the bromoketone 53, in which R is methyl, with 4-(4-hydroxybenzyl)piperidine, 44, to afford the amine 75, in which R is methyl.**



Using the conditions of Preparation 34, **44** and **53** are reacted to produce  
10 the amine **75** in which R is methyl.

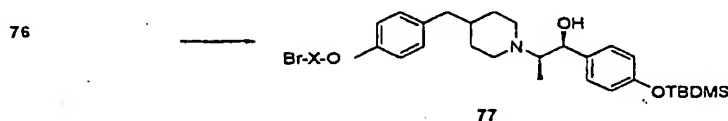
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**Preparation 51: Alkylation of the phenol 75 to afford the ether 76, in which X is  $(\text{CH}_2)_4$  and R is methyl.**



- A. Using the conditions of Preparation 1, equimolar quantities of the phenol 75 and 1,4-dibromobutane are reacted to afford the ether 76 in which X is  $(\text{CH}_2)_4$  and R is methyl.
- B. In a similar manner, by employing  $\text{Br}(\text{CH}_2)_{18}\text{Br}$  or  $\text{Br}(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2\text{Br}$  in place of 1,4-dibromobutane, there are obtained the corresponding compounds 76 in which X is  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .

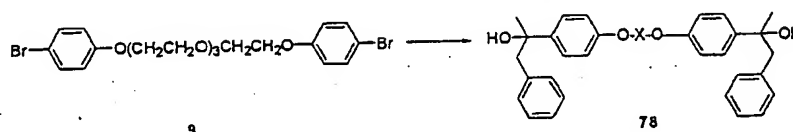
**Preparation 52: Reduction of the ketone 76, to afford the alcohol 77, in which X is  $(\text{CH}_2)_4$ .**



- A. Using the procedures of Example 9A, the ketone 76 in which X is  $(\text{CH}_2)_4$  is transformed into the alcohol 77, in which X is  $(\text{CH}_2)_4$ .
- B. Using the above procedure, but employing the ketone 76 in which X is  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ , there are obtained the corresponding compounds 77 in which X is  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .

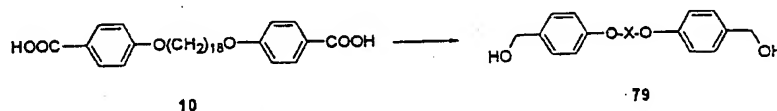
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**Preparation 53: Dimeric remacemide intermediate compound 78, in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .**



- A. The dibromide **9** (50 mmol) is dissolved in dry ether (100 mL) at  $0^\circ$  and n-BuLi in hexane (100 mmol) is added. After 1 hour, a solution of phenylacetone (50 mmol) in dry ether (30 mL) is added. The solution is left for 1 hour, then added to water. The organic solution is washed with dilute HCl, then dried and evaporated. The residue is chromatographed to afford the compound **78** in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .
- B. Using the above procedure, but employing 1,4-di-(4-bromophenoxy)butane or the dibromide **8**, in place of **9**, there are obtained the compounds **78** in which X is  $(\text{CH}_2)_4$  and  $(\text{CH}_2)_{18}$ .

**Preparation 54: Reduction of the diacid 10 to the biscarbinol 79, in which X is  $(\text{CH}_2)_{18}$ .**



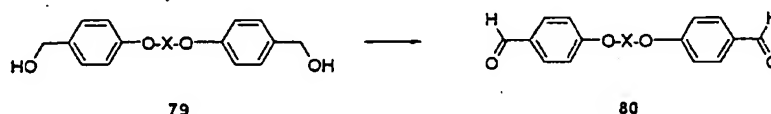
- A. The diacid **10** (50 mmol) is dissolved in THF (100 mL) at  $0^\circ$ , and a solution of LAH (100 mmol) in THF (50 mL) is added. The reaction mixture is heated to affect the reaction which is monitored by tlc. When it is complete, the excess LAH is destroyed by addition of aqueous sodium potassium tartrate, and the mixture is then extracted with EtOAc. The extract is dried and evaporated and the residue is chromatographed to afford the compound **79**, in which X is  $(\text{CH}_2)_{18}$ .



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B. Using the above procedure, but employing the diacid 1,4-di-(4-carboxyphenyl)butane or the diacid **11** in place of **10**, there are obtained the compounds **79** in which X is  $(\text{CH}_2)_4$  and  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .

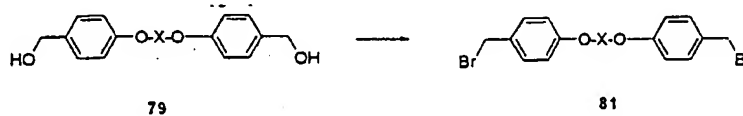
**Preparation 55: Oxidation of the biscarbinol 79 to the dialdehyde 80, in which X is  $(\text{CH}_2)_4$ .**



A. The carbinol **79**, in which X is  $(\text{CH}_2)_4$ , (50 mmol) is dissolved in  $\text{CH}_2\text{Cl}_2$  (100 mL). Pyridinium chlorochromate (110 mmol) is added in portions with stirring. The progress of the reaction is monitored by tlc. When it is complete, the solution is filtered through a small plug of silica gel, then evaporated under vacuum. The residue is chromatographed to afford the compound **80**, in which X is  $(\text{CH}_2)_4$ .

B. Using the above procedure, but employing the carbinols **79** in which X is  $(\text{CH}_2)_{18}$  and  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ , there are obtained the compounds **80** in which X is  $(\text{CH}_2)_{18}$  and  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .

**Preparation 56: Conversion of the biscarbinol 79, in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ , to the dibromide 81 in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .**

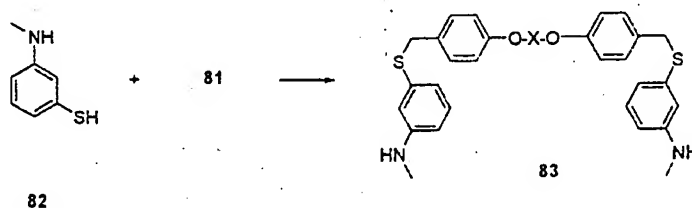


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A. Using the procedure of Preparation 26, the biscarbinol **79** is converted into the dibromide **81** in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .

B. Using the above procedure, but employing the biscarbinols **79** in which X is  $(\text{CH}_2)_4$  or  $(\text{CH}_2)_{18}$ , there are obtained the corresponding dibromides **81**.

5 **Preparation 57: Alkylation of the thiol **82** with the dibromide **81** in which X is  $(\text{CH}_2)_{18}$  to afford the thioether **83** in which X is  $(\text{CH}_2)_{18}$ .**

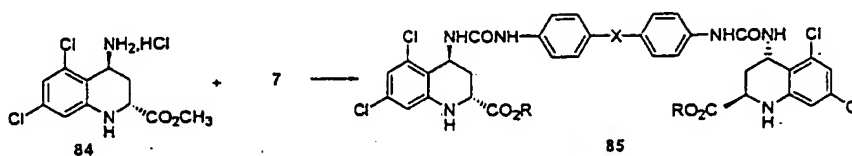


A. A solution of the dibromo compound **81** in which X is  $(\text{CH}_2)_{18}$  (50 mmol) in  $\text{CH}_2\text{Cl}_2$  (50 mL) is added over a period of 2 hours to a solution of the thiol **82**, prepared as described in South African Patent 8502022 or European Patent  
 10 123543, (100 mmol) and diisopropylethylamine (200 mmol) in  $\text{CH}_2\text{Cl}_2$  (100 mL) at  $0^\circ$ . The mixture is then left for an additional 3 hours, then the solution is washed with dilute NaOH, dried and evaporated. The residue is chromatographed to afford the compound **83** in which X is  $(\text{CH}_2)_{18}$ .

B. Using the above procedure, but employing the biscarbinols **79** in which X is  $(\text{CH}_2)_4$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ , there are obtained the corresponding  
 15 dibromides **81**.

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**Example 1: Dimeric urea analogs 85 of L-689560 in which X is  $(\text{CH}_2)_4$ ,  $(\text{CH}_2)_{18}$  and  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$  and R is H.**



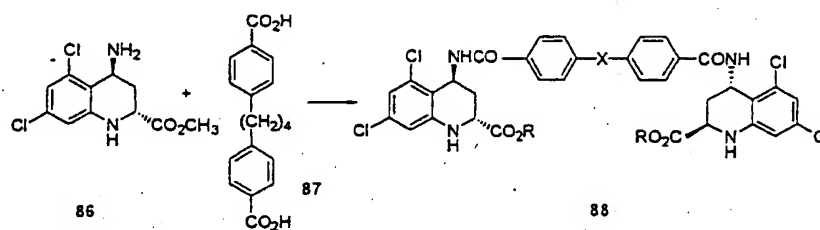
A. Methyl 4-amino-5,7-dichloro-1,2,3,4-tetrahydroquinoline-2-carboxylate hydrochloride, **84**, prepared as described in *J. Med. Chem.*, 1992, 35, 1954, (10 mmol) is suspended in  $\text{CH}_2\text{Cl}_2$  (50 mL), and  $\text{Et}_3\text{N}$  (12.5 mmol) is added. The mixture is stirred until a homogeneous solution is obtained. A solution of the diisocyanate **7** in which X is  $(\text{CH}_2)_4$ , prepared as described in Preparation 3, (5.5 mmol) in  $\text{CH}_2\text{Cl}_2$  (20 mL) is added. The progress of the reaction is monitored by tlc. When it is complete,  $\text{EtOAc}$  (100 mL) is added, and the solution is washed with 1M citric acid, then dried and evaporated. The residue is chromatographed to afford the compound **85** in which X is  $(\text{CH}_2)_4$  and R is methyl.

B. The above compound (5 mmol) is dissolved in THF (20 mL) and  $\text{LiOH}$ ,  $\text{H}_2\text{O}$  (15 mmol) in water (20 mL) is added. The progress of the reaction is monitored by tlc. When it is complete, the mixture is added to water. The pH is adjusted to 7 by addition of aqueous  $\text{NaH}_2\text{PO}_4$ . The mixture is extracted with  $\text{CH}_2\text{Cl}_2$ , and the extract is dried and evaporated. The residue is chromatographed to afford the compound **85** in which X is  $(\text{CH}_2)_4$  and R is H.

C. In a similar manner, by employing the diisocyanates **7**, in which X is  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$  in place of the diisocyanate **7** in which X is  $(\text{CH}_2)_4$ , the corresponding dimeric products **85** in which X is  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$  are obtained.

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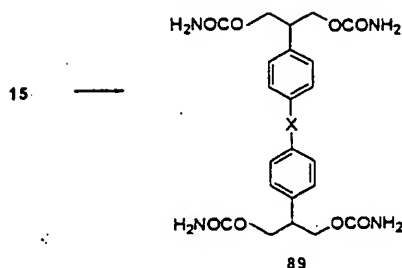
**Example 2: Dimeric amide analogs 88 of L-689560 in which X is  $(CH_2)_4$ ,  $(CH_2)_{18}$  and  $(CH_2CH_2O)_3CH_2CH_2$ .**



- A. Methyl 4-amino-5,7-dichloro-1,2,3,4-tetrahydroquinoline-2 carboxylate, **86** prepared as described in *J. Med. Chem.*, 1992, 35, 1954, ( 1 mmol) is dissolved in DMF (20 mL). Dicyclohexylcarbodiimide (2.5 mmol) and 1,4-di-(4-carboxyphenyl)butane **87**, prepared as described in US Patent 4,711,900 ( 0.55 mmol) are added. The progress of the reaction is monitored by tlc. When it is complete, the mixture is added to water and extracted with EtOAc. The extract is dried and evaporated and the residue is chromatographed to afford the compound **88**, in which X is  $(CH_2)_4$  and R is methyl.
- B. In a similar manner, by employing the diacids **10** or **11**, in place of the diacid **87**, the dimeric urea compounds **88**, in which X is  $(CH_2)_{18}$  or  $(CH_2CH_2O)_3CH_2CH_2$  and R is methyl are obtained.
- C. Using the conditions of Example 1B, the compounds **88** in which R is methyl are converted into the compounds **88** in which R is H.

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**Example 3: Dimeric analogs 89 of Felbamate in which X is  $(\text{CH}_2)_4$ ,  $(\text{CH}_2)_{18}$  and  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .**

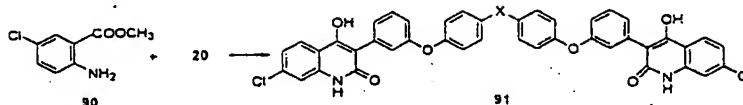


A. Using the procedure described in US Patent 5,091,595, 1,4-di-[4-(di-(1,3-dihydroxyprop-2-yl)phenyl)]butane, **15**, in which X is  $(\text{CH}_2)_4$ , obtained as  
 5 described in Preparation 9, (100 mmol) is dissolved in toluene (100 mL) and THF (30 mL) and phosgene is passed into the solution, with cooling to maintain the temperature at 25°. After 20 g of phosgene has been passed into the solution, the mixture is left for 3 hours. The solution is then added dropwise to concentrated  $\text{NH}_4\text{OH}$  (150 mL) with vigorous agitation. After 1 hour, the solvents are removed  
 10 under vacuum and the residue is stirred with water (200 mL) for 2 hours. The suspension is then filtered to afford the compound **89** in which X is  $(\text{CH}_2)_4$ .

B. In a similar manner, by employing the dimeric tetrahydroxy compounds **15**, in which X is  $(\text{CH}_2)_{18}$  and  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ , prepared as described in Preparation 9, in place of **15** in which X is  $(\text{CH}_2)_4$ , there are obtained the  
 15 corresponding compounds **89** in which X is  $(\text{CH}_2)_{18}$  and  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .

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**Example 4: Dimeric analogs 91 of L-701324, in which X is  $(\text{CH}_2)_4$ ,  $(\text{CH}_2)_{18}$  and  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .**

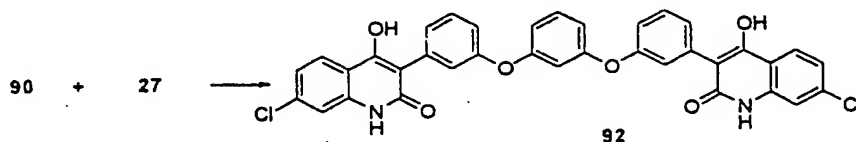


A. Methyl 5-chloroanthranilate 90 (110 mmol) is dissolved in 1,2-dichloroethane (100 mL) and to the solution is added the di-(phenylacetyl chloride) 20, the preparation of which is described in Preparation 12 (50 mmol). The mixture is heated to  $80^\circ$ , and the progress of the reaction is monitored by tlc. When it is complete, the solution is cooled and washed with dilute  $\text{Na}_2\text{CO}_3$ , then dried and evaporated. The residue is dissolved in THF (50 mL). The solution is cooled to  $0^\circ$  and a solution of potassium hexamethyldisylazide (200 mmol) in THF (50 mL) is added. The progress of the reaction is monitored by tlc. When it is complete, trifluoroacetic acid (10 mL) is added. The mixture is added to water and extracted with EtOAc. The extract is dried and evaporated, and the residue is chromatographed to afford the compound 91, in which X is  $(\text{CH}_2)_4$ .

B. In a similar manner, by employing the di-(phenylacetyl chlorides) 25, in which X is  $(\text{CH}_2)_{18}$  and  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ , the preparations of which are described in Preparation 16, in place of 20, there are obtained the corresponding compounds (91) in which X is  $(\text{CH}_2)_{18}$  and  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .

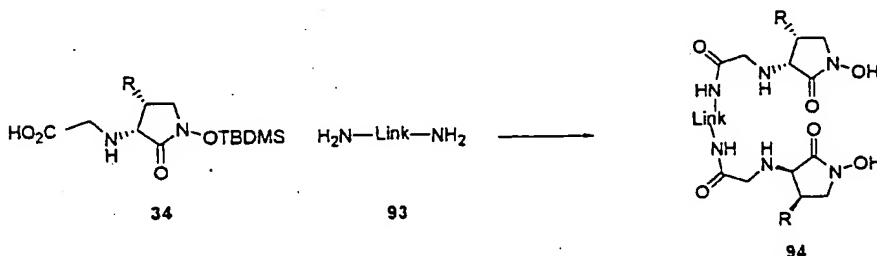
-127-

**Example 5: Dimeric analog 92 of L-701324 in which X is 1,3'-benzendiyl.**



Using the procedures of Example 4A, but employing 1,3-di-[3-(chlorocarbonylmethyl)-phenoxy]benzene, 27, prepared as described in Preparation 16, in place of the di-(phenylacetyl chloride) 20, there is obtained the dimeric compound 92.

**Example 6: Dimeric amide analogs 93 of HA 966 and L-687414, (94).**



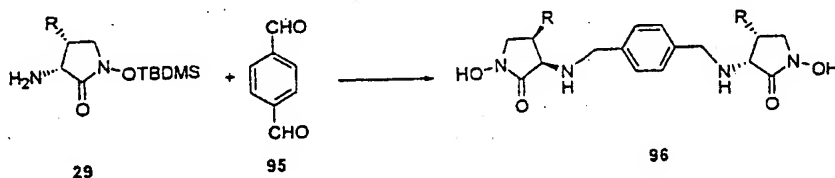
- A. The substituted glycine 34, in which R is H, the preparation of which is described in Preparation 20, (5 mmol) is dissolved in DMF (20 mL) and 1,4-diaminobutane 93 (3 mmol) and dicyclohexylcarbodiimide (6 mmol) are added.
- 10 The progress of the reaction is monitored by tlc. When it is complete, the mixture is added to water and extracted with EtOAc. The extract is dried and evaporated. The residue is dissolved in THF (25 mL) and a solution of Bu<sub>4</sub>NF (5 mmol) in THF is added. The progress of the reaction is monitored by tlc. When it is complete, the mixture is washed with water, then dried and evaporated.
- 15 The residue is chromatographed to afford the diamide compound 94, in which Link is (CH<sub>2</sub>)<sub>4</sub> and R is H.

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B. Using the above procedure, but employing the glycine derivative **34**, in which R is methyl, in place of **34** in which R is H, there is obtained the diamide compound **94** in which Link is  $(CH_2)_4$  and R is methyl.

5 C. Using the procedures of A and B above, but employing different diamines, as described herein, in place of 1,4-diaminobutane, there are obtained the corresponding compounds **94**

**Example 7: Reductive coupling of HA 966 and L-687414 derivatives to afford the dimeric compounds 96**



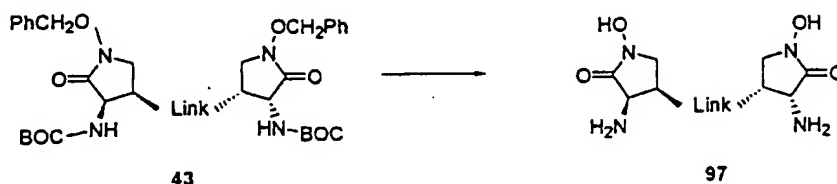
10 A. Using the procedure described in *J. Org. Chem.*, 1985, 49, 1927,  $NaBH_3CN$  (1 mmol) is dissolved in MeOH (3 mL) and to the solution is added  $ZnCl_2$  (1 mmol). The resulting solution is added to a solution of the amine **29** (1 mmol) and terephthalaldehyde **95**, (0.5 mmol). The progress of the reaction is followed by tlc. When it is complete, the mixture is added to 1M NaOH and extracted with EtOAc. The extract is dried and evaporated, and the residue is  
15 chromatographed to afford the dimeric product **96**.

B. Using the above procedure, but employing different aliphatic or aromatic dialdehydes in place of terephthalaldehyde, there are obtained the dimeric compounds analogous to **96**.



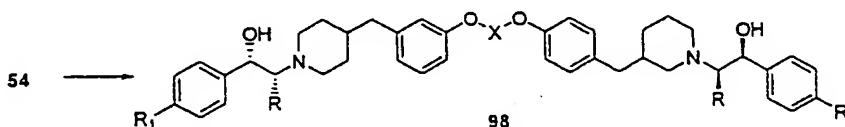
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**Example 8: Deprotection of the dimeric compound 43 to afford the L-687414 dimer 97 in which Link is  $(CH_2)_4$ .**



- A. The O-benzyl N-BOC protected dimer **43**, in which Link is  $(CH_2)_4$ , prepared as described in Preparation 28A, (0.5 mmol) is dissolved in MeOH (10 mL). Pd(OH)<sub>2</sub> (20 mg) is added, and the mixture is stirred under an atmosphere of hydrogen. The progress of the reaction is monitored by tlc. When it is complete, the mixture is filtered and the solvent is removed under vacuum. The residue is chromatographed to afford the compound **97**, in which Link is  $(CH_2)_4$ .
- B. Using the products described in Preparation 28B, and employing the procedure of Example 8A, there are obtained the corresponding compounds **97**.

**Example 9: Reduction and deprotection of the silyl ketone 54 to afford the dimeric ether-linked Ifenprodil and Eliprodil analogs 98.**



- A. The dimeric ketone **54**, in which X is  $(CH_2)_4$ , R is methyl and R<sub>1</sub> is triisopropylsilyloxy, (10 mmol) is dissolved in EtOH (10 mL) and NaBH<sub>4</sub> (20 mmol) is added. The progress of the reaction is monitored by tlc. When it is complete, the solution is added to water and extracted with EtOAc. The extract is dried and evaporated to afford a residue.

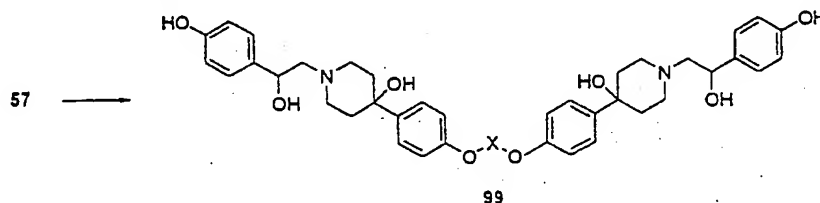
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B. The residue from A is dissolved in THF (10 mL) and a solution of  $\text{Bu}_4\text{NF}$  (15 mmol) in THF (10 mL) is added. After 1 hour, the mixture is added to water and extracted with EtOAc. The extract is dried and evaporated and the residue is chromatographed to afford the compound 98, in which X is  $(\text{CH}_2)_4$ , R is methyl and  $\text{R}_1$  is OH.

C. Using procedures A and B above, but employing the compounds 54 in which X is  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ , there are obtained the compounds 98 in which X is  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ . R is methyl and  $\text{R}_1$  is OH.

D. Using procedure A above, but employing the compound 54 in which X is  $(\text{CH}_2)_4$ , R is H and  $\text{R}_1$  is Cl, there is obtained a residue which is chromatographed to afford the compound 98 in which X is  $(\text{CH}_2)_4$  and  $\text{R}_1$  is Cl. Alternatively, employing the compound 54 in which X is  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ . R is H and  $\text{R}_1$  is Cl, there is obtained a residue which is chromatographed to afford the compound 98 in which X is  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ , R is H and  $\text{R}_1$  is Cl.

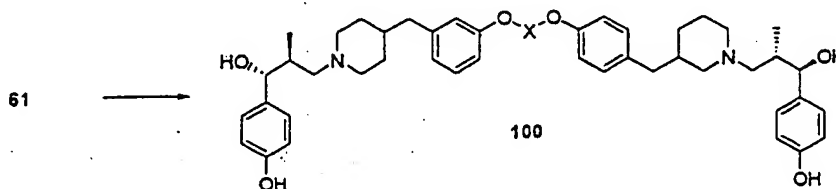
Example 10: Reduction and deprotection of the silyl ketones 57 to afford the dimeric CP-101606 analogs 99, in which X is  $(\text{CH}_2)_4$ ,  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .



Using the procedures of Examples 9A and 9B, the compounds 57 in which X is  $(\text{CH}_2)_4$ ,  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$  are converted into the compounds 99 in which X is  $(\text{CH}_2)_4$ ,  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .

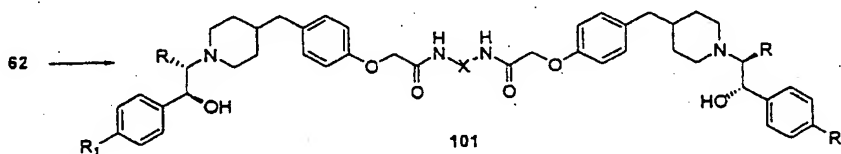
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**Example 11: Reduction and deprotection of the silyl ketones 61, to afford the dimeric RO-25-6981 analogs 100, in which X is  $(\text{CH}_2)_4$ ,  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .**



Using the procedures of Examples 9A and 9B, the compounds 61, in which  
 5 X is  $(\text{CH}_2)_4$ ,  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ , are converted into the compounds  
 100 in which X is  $(\text{CH}_2)_4$ ,  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .

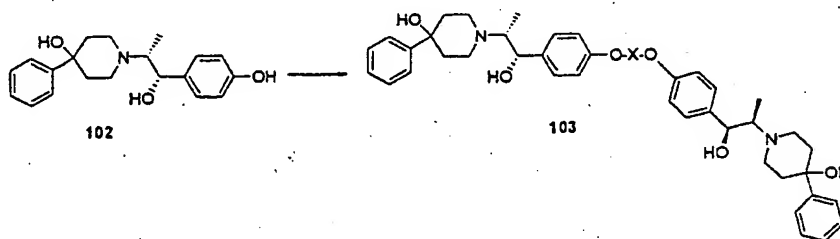
**Example 12: Reduction and deprotection of the silyl ketone 62, to afford the dimeric amide-linked Ifenprodil and Eliprodil analogs 101.**



Using the procedure of Examples 9A and, if appropriate, that of Example  
 10 9B, the compounds 62 in which X is  $(\text{CH}_2)_4$ ,  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ , R is  
 methyl or H, and  $\text{R}_1$  is triisopropylsilyloxy or Cl, are converted into the  
 compounds 101, in which X is  $(\text{CH}_2)_4$ ,  $(\text{CH}_2)_{18}$  or  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ , R is  
 methyl or H, and  $\text{R}_1$  is OH or Cl.

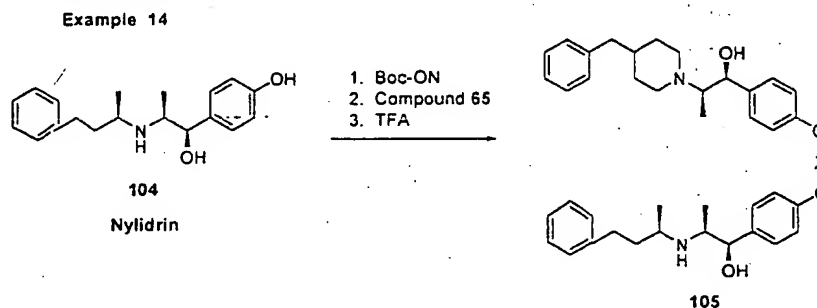
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**Example 13: Alkylation of CP-101606 (102) with 1,11-dibromo-3,6,9-trioxaundecane to afford the dimeric ether (103) in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .**



- A. Using the conditions of Preparation 2, CP-101606, **102**, is converted into the dimeric ether **103** in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .
- B. Using the above conditions, but employing different dialkylating agents, as described herein, for example 1,4-dibromobutane or 1,18-dibromooctadecane, in place of 1,11-dibromo-3,6,9-trioxaundecane, there are obtained the corresponding compounds **103** in which X is  $(\text{CH}_2)_4$  or  $(\text{CH}_2)_{18}$ .
- C. Using the above conditions, but employing different phenolic starting materials in place of CP-101606, such as Ifenprodil **63** or RO-25-6981 **66**, the corresponding dimeric ethers are obtained.

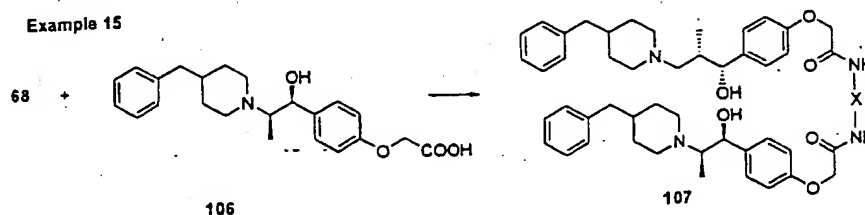
**Example 14: Alkylation of Nyldrin (104), with the Ifenprodil tosylate 65, to afford the heterodimeric ether 105 in which X is  $(\text{CH}_2)_4$ .**



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- A. Nylidrin **104** (0.2 mol) is dissolved in  $\text{CH}_2\text{Cl}_2$  (200 mL). BOC-  
 $\text{ON}=\text{C}(\text{CN})\text{Ph}$ , obtained from the Aldrich Chemical Co., (0.22 mol) and  $\text{Et}_3\text{N}$   
 (0.50 mol) are added and the progress of the reaction is monitored by tlc. When it  
 is complete, the solution is washed with dilute HCl, then dried and evaporated.
- 5 Boc Nylidrin is purified by chromatography.
- B. Using the conditions of Preparation 1, equimolar amounts of Boc Nylidrin  
 and the tosylate **65** are reacted together to afford the di-Boc protected form of  
 dimeric ether **105** in which X is  $(\text{CH}_2)_4$ .
- C. Di-Boc **105** (1 mmol) is dissolved in TFA (10 mL). The progress of the  
 10 reaction is monitored by tlc. When it is complete, the TFA is removed under  
 vacuum, and the residue is chromatographed to afford the compound **105**, in which  
 X is  $(\text{CH}_2)_4$ .
- D. Using the above conditions, but employing the tosylates **65** in which X is  
 $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$  or  $(\text{CH}_2)_{18}$  the corresponding dimeric ethers **105** in which X  
 15 is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$  or  $(\text{CH}_2)_{18}$  are obtained.

**Example 15: Amide formation between the amine 68, derived from RO-25-6981, and the oxyacetic acid 106 derived from Ifenprodil to afford the heterodimer 107 in which X is  $(\text{CH}_2)_4$ .**

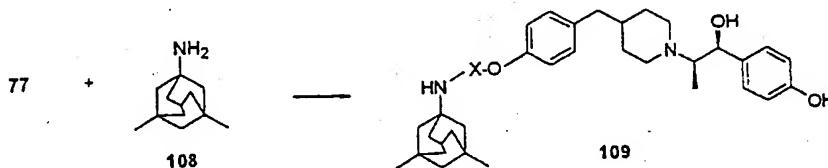


- The amine **68**, in which X is  $(\text{CH}_2)_4$  (100 mmol) is dissolved in DMF (50  
 20 mL) and the Ifenprodil oxyacetic acid. **106**, prepared as described in Preparation

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43D (100 mmol), and dicyclohexylcarbodiimide (100 mmol) are added. The progress of the reaction is monitored by tlc. When it is complete, the mixture is added to water and extracted with EtOAc. The extract is dried and evaporated, and the residue is chromatographed to afford the compound **107** in which X is  $(\text{CH}_2)_4$ .

**Example 16: Dimeric amine 109, in which X is  $(\text{CH}_2)_4$ , incorporating the Memantidine and Eliprodil ligands.**

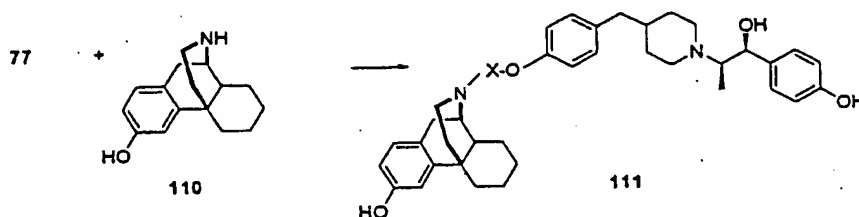


A. The bromoether **77**, in which X is  $(\text{CH}_2)_4$  (50 mmol) is dissolved in MeCN (30 mL), and memantidine (**108**) (200 mmol) and KI (25 mg) are added. The progress of the reaction is monitored by tlc. When it is complete, the mixture is added to water and extracted with  $\text{CH}_2\text{Cl}_2$ . The extract is washed with water, then dried and evaporated. The residue is dissolved in THF (50 mL) and a solution of  $\text{Bu}_4\text{NF}$  (50 mmol) in THF (50 mL) is added. After 1 hour, the solution is added to water and extracted with  $\text{CH}_2\text{Cl}_2$ . The extract is dried and evaporated, and the residue is chromatographed to afford the compound **109** in which X is  $(\text{CH}_2)_4$ .

B. Using the above procedure, the bromoethers **77** in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$  or  $(\text{CH}_2)_{18}$  are converted into the compounds **109** in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$  or  $(\text{CH}_2)_{18}$ .

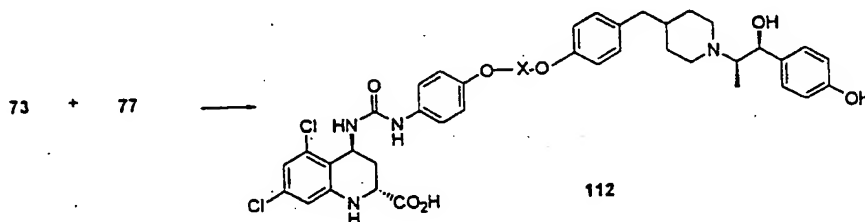
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**Example 17: Dimeric amine 111 in which X is (CH<sub>2</sub>)<sub>4</sub>, incorporating the Dextrorphan and Eliprodil ligands.**



- A. Using the procedure of Example 16, the bromoether 77 in which X is (CH<sub>2</sub>)<sub>4</sub>, is reacted with dextrorphan, 110, prepared as described in US Patent 3,810,899, to afford the tertiary amine compound 111, in which X is (CH<sub>2</sub>)<sub>4</sub>.
- B. Using the above procedure, the bromoethers 77 in which X is (CH<sub>2</sub>CH<sub>2</sub>O)<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub> or (CH<sub>2</sub>)<sub>18</sub> are converted into the compounds 111 in which X is (CH<sub>2</sub>CH<sub>2</sub>O)<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub> or (CH<sub>2</sub>)<sub>18</sub>.

**Example 18: Alkylation reaction to afford the ether 112, incorporating the L 689560 and Eliprodil ligands.**



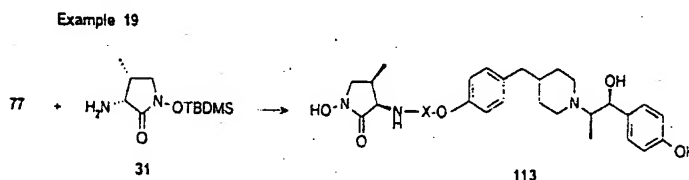
- A. The phenol 73 (50 mmol) is dissolved in MeCN (25 mL) and to the solution is added K<sub>2</sub>CO<sub>3</sub> (300 mg), KI (25 mg) and the bromoether 77 in which X is (CH<sub>2</sub>)<sub>4</sub> (50 mmol). The mixture is heated to 60° and the progress of the reaction is monitored by tlc. When it is complete, the solution is cooled and added to water. The aqueous solution is extracted with CH<sub>2</sub>Cl<sub>2</sub>. The extract is dried and evaporated, and the residue is taken up in THF. A solution of Bu<sub>4</sub>NF (100 mmol) is added. After 1 hour, the reaction mixture is added to water and is

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extracted with  $\text{CH}_2\text{Cl}_2$ . The extract is dried and evaporated, and the residue is taken up in THF (25 mL). To the solution is added LiOH,  $\text{H}_2\text{O}$  (100 mmol), in water (25 mL). The progress of the reaction is followed by tlc. When it is complete, the reaction mixture is added to water. The pH is adjusted to 7 by addition of aqueous  $\text{NaH}_2\text{PO}_4$ , and it is then extracted with  $\text{CH}_2\text{Cl}_2$ . The extract is dried and evaporated, and the residue is chromatographed to afford the compound 112, in which X is  $(\text{CH}_2)_4$ .

B. Using the above procedure, but employing the bromoethers 77 in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$  or  $(\text{CH}_2)_{18}$ , there are obtained the compounds 112 in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$  or  $(\text{CH}_2)_{18}$ .

**Example 19:** The dimeric ether 113, in which the ligands of Ifenprodil and HA 966 or L-687414 are connected.



A. Using the procedure of Preparation 47, the bromoether 77 in which X is  $(\text{CH}_2)_{18}$  is reacted with the silylated amine 31 in which R is H, to afford an intermediate bis (silyl ether). This compound is treated under the conditions of Example 9B to remove the silyl protecting groups and afford the compound 113 in which X is  $(\text{CH}_2)_{18}$  and R is H.

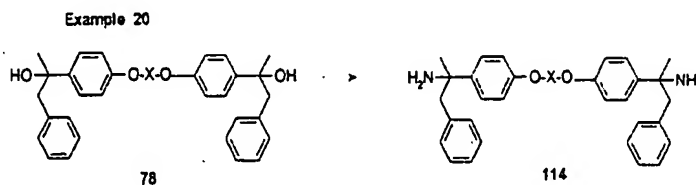
B. Using the above procedure, but employing the amine 31 in which R is methyl, there is obtained the corresponding compound 113 in which X is  $(\text{CH}_2)_{18}$  and R is methyl.



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C. Using the above procedures, but employing the bromoethers 77 in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$  or  $(\text{CH}_2)_{18}$ , there are obtained the corresponding dimeric compounds 113 in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$  or  $(\text{CH}_2)_{18}$ .

**Example 20: Ether-linked dimer 114, in which X is  $(\text{CH}_2)_{18}$ , of the amine metabolite of Remacemide.**



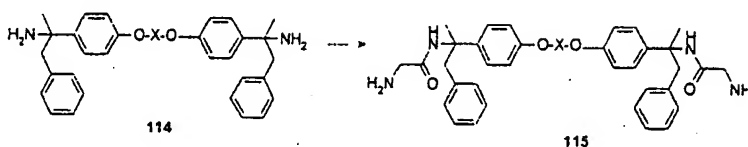
A. Using the procedure described in US Patent 5,093,524, sodium cyanide (300 mmol) is suspended in AcOH (300 mL) and n-butyl ether (60 mL) at  $0^\circ$ , and  $\text{H}_2\text{SO}_4$  (70 mL) is added in portions over a period of 20 minutes. The ice bath is removed and a solution of the biscarbinol 78 in which X is  $(\text{CH}_2)_{18}$  (100 mmol) in n-butyl ether (50 mL) is added over a period of 2 hours. The progress of the reaction is monitored by tlc. When it is complete, the mixture is poured on to ice and extracted with  $\text{CH}_2\text{Cl}_2$ . The extract is dried and evaporated, and the residue, containing the N-formyl derivative of the final product, is suspended in 1N HCl (250 mL) and the solution is heated at reflux for 2 hours. The solution is cooled and basified with aqueous NaOH, then extracted with  $\text{CH}_2\text{Cl}_2$ . The extract is dried and evaporated, and the residue is chromatographed to afford the compound 114, in which X is  $(\text{CH}_2)_{18}$ .

B. Using the above procedure, the biscarbinols 78, in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$  or  $(\text{CH}_2)_4$  are converted into the compounds 114 in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$  or  $(\text{CH}_2)_4$ .

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**Example 21: Remacemide ether-linked dimer 115, in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .**

Example 21

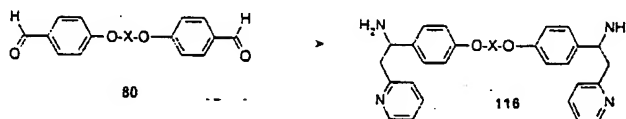


- A. The amine **114** in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ , prepared as described in Example 20B, (10 mmol) is dissolved in dry THF (50 mL) containing diisopropylethylamine (30 mmol) and the solution is cooled to  $-40^\circ$ . A solution of bromoacetyl chloride (25 mmol) in THF (15 mL) is added. The progress of the reaction is monitored by tlc. When it is complete, a solution of ammonia (3 g) in THF (100 mL) is added with vigorous stirring. The progress of the reaction is monitored by tlc. When it is complete, the mixture is added to water and extracted with  $\text{CH}_2\text{Cl}_2$ . The extract is dried and evaporated and the residue is chromatographed to afford the compound **115** in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .

- B. Using the above procedure, the amines **114**, in which X is  $(\text{CH}_2)_4$  or  $(\text{CH}_2)_{18}$ , are converted into the compounds **115** in which X is  $(\text{CH}_2)_4$  or  $(\text{CH}_2)_{18}$ .

- Example 22: Ether-linked dimer 116 of ARL 15896AR, in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$ .**

Example 22



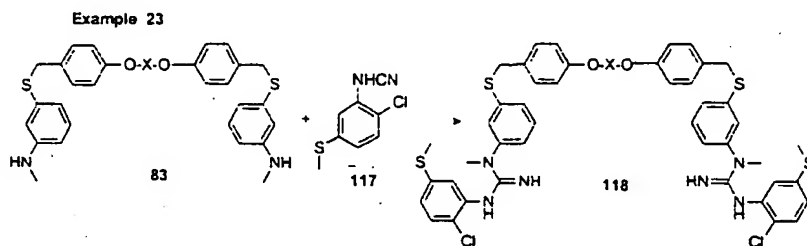
- A. Using the procedure described in WO 9422831, the dialdehyde **80** in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$  (30 mmol) is dissolved in dry THF (75 mL) and the solution is cooled to  $0^\circ$ . A solution of lithium bis(trimethylsilyl) amide (60 mmol)

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in THF (50 mL) is added over 30 minutes. The mixture is maintained at 0° for 3 hours. To a separate flask containing a solution of 2-picoline (60 mmol) in THF (50 ml), at -78°, n-BuLi (60 mL of a 1M solution in hexane, 60 mmol) is added over a period of 20 minutes. This solution, containing the anion of 2-picoline, is cannulated into the first reaction mixture, and cooled to 0° over a period of 20 minutes. The cooling bath is removed and after 1 hour the mixture is added to excess dilute HCl. The aqueous solution is washed with ether, then made basic with aqueous NaOH. The basic solution is extracted with CH<sub>2</sub>Cl<sub>2</sub>. The extract is dried and evaporated to afford a residue which upon chromatography affords the amine **116**, in which X is (CH<sub>2</sub>CH<sub>2</sub>O)<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>.

B. Using the above procedure, the dialdehydes **80** in which X is (CH<sub>2</sub>)<sub>4</sub> or (CH<sub>2</sub>)<sub>18</sub> are converted into the compounds **116** in which X is (CH<sub>2</sub>)<sub>4</sub> or (CH<sub>2</sub>)<sub>18</sub>.

**Example 23: Ether-linked dimer 118, in which X is (CH<sub>2</sub>)<sub>18</sub>, of the ligand of CNS-5161.**



A. The hydrochloride of the diamine **83**, in which X is (CH<sub>2</sub>)<sub>18</sub> (10 mmol), and the cyanamide **117**, prepared as described in *J. Med. Chem.*, 1997, 40, 4281, (12 mmol) are heated at 140-150° in chlorobenzene (10 mL) under nitrogen with stirring. The progress of the reaction is monitored by tlc. When it is complete, the solvent is removed under vacuum and the residue is chromatographed to afford the compound **118** in which X is (CH<sub>2</sub>)<sub>18</sub>.

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B. Using the above procedure, the diamines **83** in which X is  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$  or  $(\text{CH}_2)_4$  are converted into the compounds **118** in which  $(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_2\text{CH}_2$  or  $(\text{CH}_2)_4$ .

5 The above examples are illustrative only and are not meant to be indicative of the scope of the invention, which is set forth in the claims below. Those skilled in the art will recognize alternative methods and materials which may be used within the scope of the invention.

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**WHAT IS CLAIMED IS:**

1. A multibinding compound represented by Formula I:



and pharmaceutically acceptable salts thereof;

5 wherein:

each L is a ligand that may be the same or different at each occurrence;

each X is a linker that may be the same or different at each occurrence;

p is an integer of from 2 to 10; and

q is an integer of from 1 to 20;

10 wherein each of said ligands comprises a ligand domain capable of binding to a NMDA receptor, and where q is less than p.

2. The multibinding compound of claim 1, wherein each of said ligands is capable of modulating cation transport activity of the NMDA receptor.

15 3. The multibinding compound of claim 2, wherein each ligand capable of binding to an NMDA receptor is independently selected from the group consisting of glycine antagonists, glycine partial agonists, glutamate antagonists, polyamines, ion channel blockers and redox site binders.

4. The multibinding compound of claim 3, wherein at least one ligand is  
20 selected from the group consisting of L 689560, felbamate, L-701324, HA 966, L-687414, ifenprodil, eliprodil, RO-25-6981, nylidrin, SYM 2030, cycloserine, CGP-37489, CP-101606, arcaine, memantidine, dextrophan, detromethorphan, remacemide, ketamine, ARL 15896AR, aptiganel, MK801, CNS-5161, selfotel, flupertine, SDZ EAA 494, ketobemidone, MDL 10043, CGP-40116, NPC 12626,  
25 FR 115427, MDL 27266, licostinel, L-705022, BIII 227Cl, or derivatives thereof

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5. The multibinding compound of claim 3, wherein at least one ligand is selected from the group consisting of dexanabinol, midafotel, RO-24-6173, RO-8-4304, GPI-3000, ADCI, FPL-16283, LY-274614, WAY-126090, HO-473, CNS-1531, CP-98113, ES-2421, CNS-1044, CNS-5065, CNS-1118, CNS-1524, CNS-1505, L-701315, L-701376, L-701252, L-698532, L-687414, L-701273, LY-235959, LY-233053, LY-235723, LY-233536, EMD-95885, CGP-39653, MRZ-2/579, CP-101616, AP-6, NC-1210, PD-158473, NPS-1506 or derivatives thereof.
6. The multibinding compound of claim 2, wherein each divalent linker X is independently selected from a structure of Table 1.
7. The multibinding compound of claim 6, wherein  $p$  is an integer of from 2 to 4, and  $q$  is less than  $p$ .
8. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a therapeutically effective amount of one or more multibinding compounds represented by Formula I,
- $$(L)_p(X)_q \quad (I)$$
- and pharmaceutically acceptable salts thereof;
- wherein:
- each L is a ligand that may be the same or different at each occurrence;
  - each X is a linker that may be the same or different at each occurrence;
  - $p$  is an integer of from 2 to 10; and
  - $q$  is an integer of from 1 to 20;
- wherein each of said ligands comprises a ligand domain capable of binding to a NMDA receptor, and where  $q$  is less than  $p$ .

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9. The pharmaceutical composition of claim 8, wherein said multibinding compound or compounds is capable of modulating cation transport by the NMDA receptor to reduce pain.
10. The pharmaceutical composition of claim 9, wherein each ligand is  
 5 independently selected from the group consisting of glycine antagonists, glycine partial agonists, glutamate antagonists, polyamines, ion channel blockers and redox site binders.
11. The pharmaceutical composition of claim 10, wherein at least one ligand is  
 10 selected from the group consisting of L-689560, felbamate, L-701324, HA 966, L-687414, ifenprodil, eliprodil, RO-25-6981, nylidrin, SYM 2030, cycloserine, CGP-37489, CP-101606, arcaine, memantidine, dextrorphan, detromethorphan, remacemide, ketamine, ARL 15896AR, aptiganel, MK801, CNS-5161, selfotel, flupertine, SDZ EAA 494, ketobemidone, MDL 10043, CGP-40116, NPC 12626, FR 115427, MDL 27266, licostinel, L-705022, BIII 227Cl or derivatives thereof.
- 15 12. The pharmaceutical composition of claim 9, wherein each linker X is independently selected from a structure of Table 1.
13. The pharmaceutical composition of claim 12, wherein  $p$  is an integer of from 2 to 4, and  $q$  is less than  $p$ .
- 20 14. A method of preparing a multibinding compound represented by formula I:
- $$(L)_p(X)_q \quad (I)$$
- wherein each L is a ligand that may be the same or different at each occurrence;  
 X is a linker that may be the same or different at each occurrence;  
 $p$  is an integer of from 2 to 10; and  
 25  $q$  is an integer of from 1 to 20;

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wherein each of said ligands comprises a ligand domain capable of binding to a NMDA receptor, and where  $q$  is less than  $p$ ,

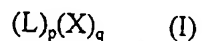
(a) providing at least  $p$  equivalents of a ligand L or precursors thereof and at least  $q$  equivalents of linker or linkers X; and

5 (b) covalently attaching said ligands to said linkers to produce a multibinding compound; or

(b') covalently attaching said ligand precursors to said linkers and completing the synthesis of said ligands thereupon, thereby to produce a multibinding compound.

10 15. The method of claim 14, wherein  $p$  is an integer of from 2 to 4, and  $q$  is less than  $p$ .

16. A method for decreasing or alleviating pain in a mammal, which method comprises administering to a mammal in need of such treatment a therapeutically effective amount of a pharmaceutical composition comprising a pharmaceutically acceptable excipient and one or more multibinding compounds represented by  
15 formula I,



and pharmaceutically acceptable salts thereof,

wherein

20 each L is a ligand that may be the same or different at each occurrence;

X is a linker that may be the same or different at each occurrence;

$p$  is an integer of from 2 to 10; and

$q$  is an integer of from 1 to 20;

25 wherein each of said ligands comprises a ligand domain capable of binding to a NMDA receptor, and where  $q$  is less than  $p$ .



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17. The method of claim 16, wherein  $p$  is an integer of from 2 to 4 and  $q$  is less than  $p$ .
18. A method for identifying multimeric ligand compounds possessing multibinding properties which method comprises:
- 5 (a) identifying a ligand or a mixture of ligands wherein each ligand contains at least one reactive functionality and has a ligand binding domain capable of binding to a NMDA receptor;
- (b) identifying a library of linkers wherein each linker in said library comprises at least two functional groups having complementary reactivity to at least
- 10 one of the reactive functional groups of the ligand;
- (c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the ligand or mixture of ligands identified in (a) with the library of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said
- 15 linker and at least two of said ligands; and
- (d) assaying the multimeric ligand compounds produced in the library prepared in (c) above to identify multimeric ligand compounds possessing multibinding properties.
19. A method for identifying multimeric ligand compounds possessing
- 20 multibinding properties which method comprises:
- (a) identifying a library of ligands wherein each ligand contains at least one reactive functionality and has a ligand binding domain capable of binding to a NMDA receptor;
- (b) identifying a linker or mixture of linkers wherein each linker
- 25 comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand;

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(c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the library of ligands identified in (a) with the linker or mixture of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands; and

(d) assaying the multimeric ligand compounds produced in the library prepared in (c) above to identify multimeric ligand compounds possessing multibinding properties.

20. The method according to Claim 18 or 19 wherein the preparation of the multimeric ligand compound library is achieved by either the sequential or concurrent combination of the two or more stoichiometric equivalents of the ligands identified in (a) with the linkers identified in (b).

21. The method according to Claim 20 wherein the multimeric ligand compounds comprising the multimeric ligand compound library are dimeric.

15 22. The method according to Claim 21 wherein the dimeric ligand compounds comprising the dimeric ligand compound library are heterodimeric.

23. The method according to Claim 22 wherein the heterodimeric ligand compound library is prepared by sequential addition of a first and second ligand.

20 24. The method according to Claim 18 or 19 wherein, prior to procedure (d), each member of the multimeric ligand compound library is isolated from the library.

25. The method according to Claim 24 wherein each member of the library is isolated by preparative liquid chromatography mass spectrometry (LCMS).

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26. The method according to Claim 18 or Claim 19 wherein the linker or linkers employed are selected from the group comprising flexible linkers, rigid linkers, hydrophobic linkers, hydrophilic linkers, linkers of different geometry, acidic linkers, basic linkers, linkers of different polarization and/or polarizability and amphiphilic linkers.
27. The method according to Claim 26 wherein the linkers comprise linkers of different chain length and/or having different complementary reactive groups.
28. The method according to Claim 27 wherein the linkers are selected to have different linker lengths ranging from about 2 to 100Å.
29. The method according to Claim 18 or 19 wherein the ligand or mixture of ligands is selected to have reactive functionality at different sites on said ligands.
30. The method according to Claim 29 wherein said reactive functionality is selected from the group consisting of carboxylic acids, carboxylic acid halides, carboxyl esters, amines, halides, pseudohalides, isocyanates, vinyl unsaturation, ketones, aldehydes, thiols, alcohols, anhydrides, boronates, and precursors thereof wherein the reactive functionality on the ligand is selected to be complementary to at least one of the reactive groups on the linker so that a covalent linkage can be formed between the linker and the ligand.
31. The method according to Claim 18 or Claim 19 wherein the multimeric ligand compound library comprises homomeric ligand compounds.
32. The method according to Claim 18 or Claim 19 wherein the multimeric ligand compound library comprises heteromeric ligand compounds.

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33. A library of multimeric ligand compounds which may possess multivalent properties which library is prepared by the method comprising:

(a) identifying a ligand or a mixture of ligands wherein each ligand contains at least one reactive functionality and has a ligand binding domain capable of binding to a NMDA receptor;

(b) identifying a library of linkers wherein each linker in said library comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand; and

(c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the ligand or mixture of ligands identified in (a) with the library of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands.

34. A library of multimeric ligand compounds which may possess multivalent properties which library is prepared by the method comprising:

(a) identifying a library of ligands wherein each ligand contains at least one reactive functionality and has a ligand binding domain capable of binding to a NMDA receptor;

(b) identifying a linker or mixture of linkers wherein each linker comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand; and

(c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the library of ligands identified in (a) with the linker or mixture of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands.

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35. The library according to Claim 33 or Claim 34 wherein the linker or linkers employed are selected from the group comprising flexible linkers, rigid linkers, hydrophobic linkers, hydrophilic linkers, linkers of different geometry, acidic linkers, basic linkers, linkers of different polarization and/or polarizability and  
5 amphiphilic linkers.
36. The library according to Claim 35 wherein the linkers comprise linkers of different chain length and/or having different complementary reactive groups.
37. The library according to Claim 36 wherein the linkers are selected to have different linker lengths ranging from about 2 to 100Å.
- 10 38. The library according to Claim 33 or 34 wherein the ligand or mixture of ligands is selected to have reactive functionality at different sites on said ligands.
39. The library according to Claim 38 wherein said reactive functionality is selected from the group consisting of carboxylic acids, carboxylic acid halides, carboxyl esters, amines, halides, pseudohalides, isocyanates, vinyl unsaturation,  
15 ketones, aldehydes, thiols, alcohols, anhydrides, boronates, and precursors thereof wherein the reactive functionality on the ligand is selected to be complementary to at least one of the reactive groups on the linker so that a covalent linkage can be formed between the linker and the ligand.
40. The library according to Claim 33 or Claim 34 wherein the multimeric  
20 ligand compound library comprises homomeric ligand compounds.
41. The library according to Claim 33 or Claim 34 wherein the multimeric ligand compound library comprises heteromeric ligand compounds.

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42. An iterative method for identifying multimeric ligand compounds possessing multibinding properties which method comprises:

- (a) preparing a first collection or iteration of multimeric compounds which is prepared by contacting at least two stoichiometric equivalents of the ligand or mixture of ligands which target a NMDA receptor with a linker or mixture of linkers wherein said ligand or mixture of ligands comprises at least one reactive functionality and has a ligand binding domain capable of binding to a NMDA receptor, and said linker or mixture of linkers comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand wherein said contacting is conducted under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands;
- (b) assaying said first collection or iteration of multimeric compounds to assess which if any of said multimeric compounds possess multibinding properties;
- (c) repeating the process of (a) and (b) above until at least one multimeric compound is found to possess multibinding properties;
- (d) evaluating what molecular constraints imparted or are consistent with imparting multibinding properties to the multimeric compound or compounds found in the first iteration recited in (a)- (c) above;
- (e) creating a second collection or iteration of multimeric compounds which elaborates upon the particular molecular constraints imparting multibinding properties to the multimeric compound or compounds found in said first iteration;
- (f) evaluating what molecular constraints imparted or are consistent with imparting enhanced multibinding properties to the multimeric compound or compounds found in the second collection or iteration recited in (e) above;
- (g) optionally repeating steps (e) and (f) to further elaborate upon said molecular constraints.

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43. The method according to Claim 42 wherein steps (e) and (f) are repeated from 2-50 times.

44. The method according to Claim 42 wherein steps (e) and (f) are repeated from 5-50 times.

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US99/12727

<b>A. CLASSIFICATION OF SUBJECT MATTER</b>		
IPC(6) : Please See Extra Sheet.		
US CL : Please See Extra Sheet.		
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b>		
Minimum documentation searched (classification system followed by classification symbols)		
U.S. : 424/1.11, 9.1, 178.1, 193.1; 435/7.1, 7.2; 436/501, 518; 530/345, 389.1, 402, 807		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
APS, STN (CAPLUS, BIOSIS, MEDLINE, SCISEARCH, EMBASE)		
Search Terms: NMDA, multivalent, combinatorial, ligand, receptor		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y, P	GEE et al. Cyclic Peptides as Non-carboxyl-terminal Ligands of Syntrophin PDZ Domains. J. Biol. Chem. 21 August 1998, Vol. 273, No. 34, pages 21980-21987, see entire article.	1-44
Y	FERRER-MONTIEL et al. Selected Peptides Targeted to the NMDA Receptor Channel Protect Neurons from Excitotoxic Death. Nature Biotech. March 1998, Vol. 16, pages 286-291, see entire article, especially Abstract and page 286.	1-44
Y	LI, M. Use of a Modified Bacteriophage to Probe the Interactions between Peptides and Ion Channel Receptors in Mammalian Cells. Nature Biotech. June 1997, Vol. 15, pages 559-563, See entire article, especially pages 559, 560 and 562.	1-44
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents:		
*A*	document defining the general state of the art which is not considered to be of particular relevance	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*B*	earlier document published on or after the international filing date	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*L*	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*O*	document referring to an oral disclosure, use, exhibition or other means	*A* document member of the same patent family
*P*	document published prior to the international filing date but later than the priority date claimed	
Date of the actual completion of the international search		Date of mailing of the international search report
11 AUGUST 1999		21 OCT 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231		Authorized officer <i>Maurie E. Garcia</i> MAURIE E. GARCIA
Facsimile No. (703) 305-3230		Telephone No. (703) 308-0196



## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US99/12727

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BERGERON et al. Impact of Polyamine Analogues on the NMDA Receptor. J. Med. Chem. 03 February 1995, Vol. 38, No. 3, pages 425-428, see entire article, especially Abstract and Scheme 2.	1-44
Y	WO 92/05802 A1 (NEORX CORPORATION) 16 April 1992 (16/04/92), see Abstract, page 3 lines 1-25, page 4 lines 20-27, page 5 lines 6-18, page 21 lines 4-33, page 22 lines 1-8 and claim 1.	1-44
Y	SHUKER et al. Discovering High-Affinity Ligands for Proteins: SAR by NMR. Science. 29 November 1996, Vol. 274, pages 1531-1534, see entire article, especially Figure 1.	18-44

INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US99/12727

A. CLASSIFICATION OF SUBJECT MATTER:  
IPC (6):

A61K 38/00, 39/00, 39/44, 39/395, 51/00; C07K 2/00, 4/00; G01N 33/53, 33/543, 33/566

A. CLASSIFICATION OF SUBJECT MATTER:  
US CL :

424/1.11, 9.1, 178.1, 193.1; 435/7.1, 7.2; 436/501, 518; 530/345, 389.1, 402, 807